Supplementary Material*

Khan SU, Khan MU, Riaz H, et al. Effects of nutritional supplements and dietary interventions on cardiovascular outcomes. An umbrella review and evidence map. Ann Intern Med. 2019. doi:10.7326/M19-0341

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* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

Supplement Table 1: Search Strategy (PubMed):

<table>
<tr><th colspan="3">Literature search till March, 2019 for meta-analyses</th></tr>
<tr><td>Search string for meta-analyses
(Results = 498)</td><td colspan="2">(("minerals"[MeSH Terms] OR "minerals"[All Fields]) OR ("vitamins"[Pharmacological Action] OR "vitamins"[MeSH Terms] OR "vitamins"[All Fields]) OR ("diet"[MeSH Terms] OR "diet"[All Fields]) AND (("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]) AND outcomes[All Fields])) AND ((meta analyis[All Fields] OR meta analyisis[All Fields] OR meta analysable[All Fields] OR meta analysas[All Fields] OR meta analyse[All Fields] OR meta analysed[All Fields] OR meta analysei[All Fields] OR meta analysen[All Fields] OR meta analyser[All Fields] OR meta analysers[All Fields] OR meta analyses[All Fields] OR meta analysescohort[All Fields] OR meta analysespublication[All Fields] OR meta analysestype[All Fields] OR meta analysi[All Fields] OR meta analysia[All Fields] OR meta analysic[All Fields] OR meta analysing[All Fields] OR meta analysis[All Fields] OR meta analysis's[All Fields] OR meta analysis,[All Fields] OR meta analysis2[All Fields] OR meta analysis2011[All Fields] OR meta analysisas[All Fields] OR meta analysisbone[All Fields] OR meta analysisc[All Fields] OR meta analysisdagger[All Fields] OR meta analysises[All Fields] OR meta analysisevaluating[All Fields] OR meta analysisif[All Fields] OR meta analysisindicated[All Fields] OR meta analysisintroduction[All Fields] OR meta analysisjr[All Fields] OR meta analysismethods[All Fields] OR meta analysismoderate[All Fields] OR meta analysisof[All Fields] OR meta analysistrade[All Fields] OR meta analysisv[All Fields] OR meta analysiswas[All Fields] OR meta analysisxs[All Fields] OR meta analysized[All Fields] OR meta analyst[All Fields] OR meta analysticians[All Fields] OR meta analysts[All Fields] OR meta analysys[All Fields] OR meta analytic[All Fields] OR meta analytical[All Fields] OR meta analytically[All Fields] OR meta analytics[All Fields] OR meta analytischer[All Fields] OR meta analyysit[All Fields] OR meta analyza[All Fields] OR meta analyzability[All Fields] OR meta analyzable[All Fields] OR meta analyze[All Fields] OR meta analyzed[All Fields] OR meta analyzes[All Fields] OR meta analyzing[All Fields]) OR (metaanalys[All Fields] OR metaanalyse[All Fields] OR metaanalysed[All Fields] OR metaanalysen[All Fields] OR metaanalyser[All Fields] OR metaanalyses[All Fields] OR metaanalyses'[All Fields] OR metaanalysis[All Fields] OR metaanalysis'[All Fields] OR metaanalysisbased[All Fields] OR metaanalysisdata[All Fields] OR metaanalyst[All Fields] OR metaanalytic[All Fields] OR metaanalytical[All Fields] OR metaanalytically[All Fields] OR metaanalytique[All Fields] OR metaanalytische[All Fields] OR metaanalytischen[All Fields] OR metaanalytischer[All Fields] OR metaanalytisk[All Fields] OR metaanalyza[All Fields] OR metaanalyze[All Fields] OR metaanalyzed[All Fields] OR metaanalyzedall[All Fields] OR metaanalyzing[All Fields] OR metaanalyzy[All Fields]) OR (systematic review[All Fields] OR systematic review,[All Fields] OR systematic reviewbeta[All Fields] OR systematic reviewer[All Fields] OR systematic reviewers[All Fields] OR systematic reviewing[All Fields] OR systematic reviewn[All Fields] OR systematic reviewobjective[All Fields] OR systematic reviews[All Fields] OR systematic reviewvsp[All Fields])) AND (("0001/01/01"[PDAT] : "2019/03/01"[PDAT]) AND "humans"[MeSH Terms])</td></tr>
<tr><th colspan="3">Literature search timelines of selected systematic reviews</th></tr>
<tr><th>Author (Year), Journal</th><th>Selected intervention(s)</th><th>Search timeline</th></tr>
<tr><td>Jenkins D et al., (2018) (1), Journal of American College of Cardiology</td><td>Antioxidants; β-carotene; vitamin B-complex; multivitamins; selenium; vitamin A; vitamin B3/Niacin;</td><td>01/2012- 10/2017</td></tr>
</table>

	vitamin B6; vitamin C; vitamin E; vitamin D; calcium + vitamin D; calcium; folic acid; iron	
Riaz H et al., (2018) (2), European Journal of Preventive Cardiology	Vitamin B3/Niacin	Inception- 01/2018
Abdelhamid AS et al., (2018) (3), Cochrane Database of Systematic Reviews	n-3 LC PUFA and n- 3 (ALA) PUFA	Inception – 04/2017
Hooper L et al., (2018) (4), Cochrane Database of Systematic Reviews	n-6 PUFA	Inception – 05/2017
Liyanage T et al. (2016) (5), Plos One	Mediterranean diet	Inception – 02/2014
Adler AJ et al., (2014) (6), Cochrane Database of Systematic Reviews	Reduced salt (normotensives or hypertensives)	Inception – 05/2013
Mente A et al., (2016) (7), Lancet	Reduced salt (normotensives or hypertensives)	01/1960- 04/2016
Hooper L et al., (2011) (8), Cochrane Database of Systematic Reviews	Modified or reduced dietary fat intake	Inception – 06/2010
Hooper L et al. (2015) (9), Cochrane Database of Systematic Reviews	Reduced saturated fat intake	Inception- 03/2014
Updated search		
Search string for supplemental vitamins and minerals (Results = 446)	(dietary supplements[All Fields] OR (vitamins[All Fields] OR vitamins'[All Fields] OR vitaminsa[All Fields] OR vitaminsabcdek[All Fields] OR vitaminsfor[All Fields] OR vitaminska[All Fields] OR vitaminske[All Fields] OR vitaminskih[All Fields] OR vitaminskoj[All Fields] OR vitaminsoderzhashchikh[All Fields] OR vitaminsparenden[All Fields] OR vitaminspritzen[All Fields] OR vitaminstandard[All Fields] OR vitaminstatus[All Fields] OR vitaminstoffwechsel[All Fields] OR vitaminsubstitution[All Fields] OR vitaminsubstitutionstherapie[All Fields] OR vitaminsupplemente[All Fields] OR vitaminsupplementierung[All Fields] OR vitaminsynthese[All Fields] OR vitaminsyre[All Fields] OR vitaminszukseglete[All Fields]) OR (minerals[All Fields] OR minerals'[All Fields] OR mineralsalt[All Fields] OR mineralsalz[All Fields] OR mineralsalzausscheidung[All Fields] OR mineralsalzbader[All Fields] OR mineralsalzbestimmung[All Fields] OR mineralsalzbestimmungen[All Fields] OR mineralsalzdefizits[All Fields] OR mineralsalzdichte[All Fields] OR mineralsalze[All Fields] OR mineralsalzen[All Fields] OR mineralsalzfrage[All Fields] OR mineralsalzgehaltes[All Fields] OR mineralsalzgehaltsbestimmung[All Fields] OR mineralsalzgemischen[All Fields] OR mineralsalzlosung[All Fields] OR mineralsalzmangelerscheinungen[All Fields] OR mineralsalzmasse[All Fields] OR mineralsalzmischungen[All Fields] OR mineralsalzquelle[All Fields] OR mineralsalzverlust[All Fields] OR mineralsalzversorgung[All Fields] OR mineralsauren[All Fields] OR mineralsaurer[All Fields] OR mineralschalen[All Fields] OR mineralsdhahran[All Fields] OR mineralses[All Fields] OR mineralsfortified[All Fields] OR mineralsk[All Fields] OR mineralspiegel[All Fields] OR mineralsplus[All Fields] OR mineralstaub[All Fields] OR mineralstaubgehalt[All Fields] OR mineralstoff[All Fields] OR mineralstoffanalyse[All Fields] OR mineralstoffangebot[All Fields] OR mineralstoffausscheidung[All Fields] OR mineralstoffbedarf[All Fields] OR mineralstoffbestimmung[All Fields] OR mineralstoffbilanz[All Fields] OR mineralstoffdungung[All Fields] OR mineralstoffe[All Fields] OR mineralstoffen[All Fields] OR mineralstoffer[All Fields] OR mineralstofferganzung[All Fields] OR mineralstoffgehalf[All Fields] OR	

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	(cardiovascular disease[All Fields] OR cardiovascular disease's[All Fields] OR cardiovascular disease,[All Fields] OR cardiovascular diseased[All Fields] OR cardiovascular diseases[All Fields])) AND (Clinical Trial[ptyp] AND ("2017/01/01"[PDAT] : "2019/03/01"[PDAT]) AND "humans"[MeSH Terms])
Search string for n-3 LC PUFA and n-3 [ALA] PUFA (Results = 82)	omega 3 fatty acids[All Fields] AND ((myocardial infarction[All Fields] OR myocardial infarction,[All Fields] OR myocardial infarctionl[All Fields] OR myocardial infarctions[All Fields]) OR (stroke[All Fields] OR stroke'[All Fields] OR stroke''[All Fields] OR stroke's[All Fields] OR stroke,[All Fields] OR stroke119[All Fields] OR stroke123[All Fields] OR stroke2[All Fields] OR stroke2000[All Fields] OR stroke2010[All Fields] OR stroke34[All Fields] OR stroke4carers[All Fields] OR stroke`s[All Fields] OR strokea[All Fields] OR strokeaetiology[All Fields] OR strokeaha[All Fields] OR strokeaha118020087[All Fields] OR strokeaha118020840[All Fields] OR strokeaha118021381[All Fields] OR strokeaha118021407[All Fields] OR strokeaha118021453[All Fields] OR strokeaha118021598[All Fields] OR strokeaha118021798[All Fields] OR strokeaha118022088[All Fields] OR strokeaha118022239[All Fields] OR strokeaha118022249[All Fields] OR strokeaha118022315[All Fields] OR strokeaha118022332[All Fields] OR strokeaha118022404[All Fields] OR strokeaha118022406[All Fields] OR strokeaha118022423[All Fields] OR strokeaha118022454[All Fields] OR strokeaha118022516[All Fields] OR strokeaha118022563[All Fields] OR strokeaha118022644[All Fields] OR strokeaha118022687[All Fields] OR strokeaha118022691[All Fields] OR strokeaha118022745[All Fields] OR strokeaha118022913[All Fields] OR strokeaha118022923[All Fields] OR strokeaha118023006[All Fields] OR strokeaha118023058[All Fields] OR strokeaha118023060[All Fields] OR strokeaha118023079[All Fields] OR strokeaha118023084[All Fields] OR strokeaha118023088[All Fields] OR strokeaha118023093[All Fields] OR strokeaha118023385[All Fields] OR strokeaha118023456[All Fields] OR strokeaha118023457[All Fields] OR strokeaha118023465[All Fields] OR strokeaha118023482[All Fields] OR strokeaha118023506[All Fields] OR strokeaha118023527[All Fields] OR strokeaha118023573[All Fields] OR strokeaha118023640[All Fields] OR strokeaha118023696[All Fields] OR strokeaha118023701[All Fields] OR strokeaha118023702[All Fields] OR strokeaha118023712[All Fields] OR strokeaha118023724[All Fields] OR strokeaha118023744[All Fields] OR strokeaha118023749[All Fields] OR strokeaha118023789[All Fields] OR strokeaha118023790[All Fields] OR strokeaha118023830[All Fields] OR strokeaha118023850[All Fields] OR strokeaha118023866[All Fields] OR strokeaha118023953[All Fields] OR strokeaha118023955[All Fields] OR strokeaha118023990[All Fields] OR strokeaha118024028[All Fields] OR strokeaha118024134[All Fields] OR strokeaha118024232[All Fields] OR strokeaha118024442[All Fields] OR strokeand[All Fields] OR strokecarecontents[All Fields] OR strokecenter[All Fields] OR strokecentre[All Fields] OR strokechecklist[All Fields] OR strokeclose[All Fields] OR strokect[All Fields] OR strokectacomputed[All Fields] OR strokectcomputed[All Fields] OR strokectomy[All Fields] OR stroked[All Fields] OR strokedepartment[All Fields] OR strokedepressive[All Fields] OR strokedge[All Fields] OR strokediagnostik[All Fields] OR strokedoc[All Fields] OR strokedrabbade[All Fields] OR strokeearly[All Fields] OR strokeed[All Fields] OR strokeelicited[All Fields] OR strokeenh[All Fields] OR strokeenheten[All Fields] OR strokefall[All Fields] OR strokefobrebyggande[All Fields] OR strokefoundation[All Fields]

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Search string for n- 6 PUFA (Results = 9)	omega 6 fatty acids[All Fields] AND ((myocardial infarction[All Fields] OR myocardial infarction,[All Fields] OR myocardial infarctionl[All Fields] OR myocardial infarctions[All Fields]) OR (stroke[All Fields] OR stroke'[All Fields] OR stroke''[All Fields] OR stroke's[All Fields] OR stroke,[All Fields] OR stroke119[All Fields] OR stroke123[All Fields] OR stroke2[All Fields] OR stroke2000[All Fields] OR stroke2010[All Fields] OR stroke34[All Fields] OR stroke4carers[All Fields] OR stroke`s[All Fields] OR strokea[All Fields] OR strokeaetiology[All Fields] OR strokeaha[All Fields] OR strokeaha118020087[All Fields] OR strokeaha118020840[All Fields] OR strokeaha118021381[All Fields] OR strokeaha118021407[All Fields] OR strokeaha118021453[All Fields] OR strokeaha118021598[All Fields] OR strokeaha118021798[All Fields] OR

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Search string for Mediterranean diet (Results = 153)	(mediterranean diet[All Fields] OR mediterranean dietary[All Fields] OR mediterranean diets[All Fields]) AND ((myocardial infarction[All Fields] OR myocardial infarction,[All Fields] OR myocardial infarctionl[All Fields] OR myocardial infarctions[All Fields]) OR (stroke[All Fields] OR stroke'[All Fields] OR stroke''[All Fields] OR stroke's[All Fields] OR stroke,[All Fields] OR stroke119[All Fields] OR stroke123[All Fields] OR stroke2[All Fields] OR stroke2000[All Fields] OR stroke2010[All Fields] OR stroke34[All Fields] OR stroke4carers[All Fields] OR stroke`s[All Fields] OR strokea[All Fields] OR strokeaetiology[All Fields] OR strokeaha[All Fields] OR strokeaha118020087[All Fields] OR strokeaha118020840[All Fields] OR strokeaha118021381[All Fields] OR strokeaha118021407[All Fields] OR strokeaha118021453[All Fields] OR strokeaha118021598[All Fields] OR strokeaha118021798[All Fields] OR strokeaha118022088[All Fields] OR strokeaha118022239[All Fields] OR strokeaha118022249[All Fields] OR strokeaha118022315[All Fields] OR strokeaha118022332[All Fields] OR strokeaha118022404[All Fields] OR strokeaha118022406[All Fields] OR strokeaha118022423[All Fields] OR strokeaha118022454[All Fields] OR strokeaha118022516[All Fields] OR strokeaha118022563[All Fields] OR strokeaha118022644[All Fields] OR strokeaha118022687[All Fields] OR strokeaha118022691[All Fields] OR strokeaha118022745[All Fields] OR strokeaha118022913[All Fields] OR strokeaha118022923[All Fields] OR strokeaha118023006[All Fields] OR strokeaha118023058[All Fields] OR strokeaha118023060[All Fields] OR strokeaha118023079[All Fields] OR strokeaha118023084[All Fields] OR strokeaha118023088[All Fields] OR strokeaha118023093[All Fields] OR strokeaha118023385[All Fields] OR strokeaha118023456[All Fields] OR

	strokeaha118023457[All Fields] OR strokeaha118023465[All Fields] OR strokeaha118023482[All Fields] OR strokeaha118023506[All Fields] OR strokeaha118023527[All Fields] OR strokeaha118023573[All Fields] OR strokeaha118023640[All Fields] OR strokeaha118023696[All Fields] OR strokeaha118023701[All Fields] OR strokeaha118023702[All Fields] OR strokeaha118023712[All Fields] OR strokeaha118023724[All Fields] OR strokeaha118023744[All Fields] OR strokeaha118023749[All Fields] OR strokeaha118023789[All Fields] OR strokeaha118023790[All Fields] OR strokeaha118023830[All Fields] OR strokeaha118023850[All Fields] OR strokeaha118023866[All Fields] OR strokeaha118023953[All Fields] OR strokeaha118023955[All Fields] OR strokeaha118023990[All Fields] OR strokeaha118024028[All Fields] OR strokeaha118024134[All Fields] OR strokeaha118024232[All Fields] OR strokeaha118024442[All Fields] OR strokeand[All Fields] OR strokecarecontents[All Fields] OR strokecenter[All Fields] OR strokecentre[All Fields] OR strokechecklist[All Fields] OR strokeclose[All Fields] OR strokect[All Fields] OR strokectacomputed[All Fields] OR strokectcomputed[All Fields] OR strokectomy[All Fields] OR stroked[All Fields] OR strokedepartment[All Fields] OR strokedepressive[All Fields] OR strokedge[All Fields] OR strokediagnostik[All Fields] OR strokedoc[All Fields] OR strokedrabbade[All Fields] OR strokeearly[All Fields] OR strokeed[All Fields] OR strokeelicited[All Fields] OR strokeenh[All Fields] OR strokeenheten[All Fields] OR strokefall[All Fields] OR strokefobrebyggande[All Fields] OR strokefoundation[All Fields] OR strokefree[All Fields] OR strokefrom[All Fields] OR strokehip[All Fields] OR strokein[All Fields] OR strokeinduced[All Fields] OR strokeintracerebral[All Fields] OR strokelets[All Fields] OR strokelike[All Fields] OR strokelink[All Fields] OR strokelocated[All Fields] OR strokemerci[All Fields] OR strokemethods[All Fields] OR strokemobile[All Fields] OR stroken[All Fields] OR strokenational[All Fields] OR strokenet[All Fields] OR strokengine[All Fields] OR strokengine's[All Fields] OR strokenomics[All Fields] OR strokenomics'[All Fields] OR strokepatienter[All Fields] OR strokepatients[All Fields] OR strokepharmacogenomics[All Fields] OR strokeplane[All Fields] OR strokeprevention[All Fields] OR strokeprofylax[All Fields] OR strokeprofylaxen[All Fields] OR strokeproject[All Fields] OR strokeprone[All Fields] OR stroker[All Fields] OR strokerehab[All Fields] OR strokerehabilitering[All Fields] OR strokerisk[All Fields] OR strokers[All Fields] OR strokerwin[All Fields] OR strokes[All Fields] OR strokes'[All Fields] OR strokes1[All Fields] OR strokesafe[All Fields] OR strokesand[All Fields] OR strokesektionen[All Fields] OR strokesfuture[All Fields] OR strokesich[All Fields] OR strokeskydd[All Fields] OR strokesmin[All Fields] OR strokestop[All Fields] OR strokestra[All Fields] OR strokestudygz[All Fields] OR strokethree[All Fields] OR stroketool[All Fields] OR stroketrials[All Fields] OR strokeun[All Fields] OR strokeunit[All Fields] OR strokevan[All Fields] OR strokevard[All Fields] OR strokevarden[All Fields] OR strokevia[All Fields] OR strokevision[All Fields] OR strokevolume[All Fields] OR strokevolumedon[All Fields] OR strokevolumes[All Fields] OR strokewidth[All Fields] OR strokework[All Fields] OR strokezero[All Fields]) OR (mortality[All Fields] OR mortality'[All Fields] OR mortality''[All Fields] OR mortality's[All Fields] OR mortality,[All Fields] OR mortality1[All Fields] OR mortality12[All Fields] OR mortality19[All Fields] OR mortality1965[All Fields] OR mortality2[All Fields] OR mortalityabc[All Fields] OR mortalityagainst[All Fields] OR mortalityall[All Fields] OR mortalityand[All Fields] OR mortalityat[All Fields] OR mortalitydagger[All Fields] OR mortalityfor[All Fields] OR mortalityhf[All Fields] OR mortalityin[All Fields] OR mortalityinterval[All Fields] OR mortalityinthe[All Fields] OR

	mortalitynrmand[All Fields] OR mortalityof[All Fields] OR mortalityon[All Fields] OR mortalitypredictors[All Fields] OR mortalityrate[All Fields] OR mortalityrates[All Fields] OR mortalityrelated[All Fields] OR mortalityresearch[All Fields] OR mortalitysahsubarachnoid[All Fields] OR mortalitystudy[All Fields] OR mortalitysuggests[All Fields] OR mortalitythat[All Fields] OR mortalitythree[All Fields] OR mortalitytrm[All Fields] OR mortalitytrmin[All Fields] OR mortalitywas[All Fields] OR mortalitywith[All Fields] OR mortalityworldwide[All Fields] OR mortalityyy[All Fields]) OR (cardiovascular disease[All Fields] OR cardiovascular disease's[All Fields] OR cardiovascular disease,[All Fields] OR cardiovascular diseased[All Fields] OR cardiovascular diseases[All Fields])) AND (Clinical Trial[ptyp] AND ("2014/01/01"[PDAT] : "2019/03/01"[PDAT]) AND "humans"[MeSH Terms])
Search string for reduced salt (normotensives or hypertensives) (Results = 88)	(dietary salt[All Fields] OR dietary salts[All Fields]) AND ((myocardial infarction[All Fields] OR myocardial infarction,[All Fields] OR myocardial infarctionl[All Fields] OR myocardial infarctions[All Fields]) OR (stroke[All Fields] OR stroke'[All Fields] OR stroke''[All Fields] OR stroke's[All Fields] OR stroke,[All Fields] OR stroke119[All Fields] OR stroke123[All Fields] OR stroke2[All Fields] OR stroke2000[All Fields] OR stroke2010[All Fields] OR stroke34[All Fields] OR stroke4carers[All Fields] OR stroke`s[All Fields] OR strokea[All Fields] OR strokeaetiology[All Fields] OR strokeaha[All Fields] OR strokeaha118020087[All Fields] OR strokeaha118020840[All Fields] OR strokeaha118021381[All Fields] OR strokeaha118021407[All Fields] OR strokeaha118021453[All Fields] OR strokeaha118021598[All Fields] OR strokeaha118021798[All Fields] OR strokeaha118022088[All Fields] OR strokeaha118022239[All Fields] OR strokeaha118022249[All Fields] OR strokeaha118022315[All Fields] OR strokeaha118022332[All Fields] OR strokeaha118022404[All Fields] OR strokeaha118022406[All Fields] OR strokeaha118022423[All Fields] OR strokeaha118022454[All Fields] OR strokeaha118022516[All Fields] OR strokeaha118022563[All Fields] OR strokeaha118022644[All Fields] OR strokeaha118022687[All Fields] OR strokeaha118022691[All Fields] OR strokeaha118022745[All Fields] OR strokeaha118022913[All Fields] OR strokeaha118022923[All Fields] OR strokeaha118023006[All Fields] OR strokeaha118023058[All Fields] OR strokeaha118023060[All Fields] OR strokeaha118023079[All Fields] OR strokeaha118023084[All Fields] OR strokeaha118023088[All Fields] OR strokeaha118023093[All Fields] OR strokeaha118023385[All Fields] OR strokeaha118023456[All Fields] OR strokeaha118023457[All Fields] OR strokeaha118023465[All Fields] OR strokeaha118023482[All Fields] OR strokeaha118023506[All Fields] OR strokeaha118023527[All Fields] OR strokeaha118023573[All Fields] OR strokeaha118023640[All Fields] OR strokeaha118023696[All Fields] OR strokeaha118023701[All Fields] OR strokeaha118023702[All Fields] OR strokeaha118023712[All Fields] OR strokeaha118023724[All Fields] OR strokeaha118023744[All Fields] OR strokeaha118023749[All Fields] OR strokeaha118023789[All Fields] OR strokeaha118023790[All Fields] OR strokeaha118023830[All Fields] OR strokeaha118023850[All Fields] OR strokeaha118023866[All Fields] OR strokeaha118023953[All Fields] OR strokeaha118023955[All Fields] OR strokeaha118023990[All Fields] OR strokeaha118024028[All Fields] OR strokeaha118024134[All Fields] OR strokeaha118024232[All Fields] OR strokeaha118024442[All Fields] OR strokeand[All Fields] OR strokecarecontents[All

	Fields] OR strokecenter[All Fields] OR strokecentre[All Fields] OR strokechecklist[All Fields] OR strokeclose[All Fields] OR strokect[All Fields] OR strokectacomputed[All Fields] OR strokectcomputed[All Fields] OR strokectomy[All Fields] OR stroked[All Fields] OR strokedepartment[All Fields] OR strokedepressive[All Fields] OR strokedge[All Fields] OR strokediagnostik[All Fields] OR strokedoc[All Fields] OR strokedrabbade[All Fields] OR strokeearly[All Fields] OR strokeed[All Fields] OR strokeelicited[All Fields] OR strokeenh[All Fields] OR strokeenheten[All Fields] OR strokefall[All Fields] OR strokefobrebyggande[All Fields] OR strokefoundation[All Fields] OR strokefree[All Fields] OR strokefrom[All Fields] OR strokehip[All Fields] OR strokein[All Fields] OR strokeinduced[All Fields] OR strokeintracerebral[All Fields] OR strokelets[All Fields] OR strokelike[All Fields] OR strokelink[All Fields] OR strokelocated[All Fields] OR strokemerci[All Fields] OR strokemethods[All Fields] OR strokemobile[All Fields] OR stroken[All Fields] OR strokenational[All Fields] OR strokenet[All Fields] OR strokengine[All Fields] OR strokengine's[All Fields] OR strokenomics[All Fields] OR strokenomics'[All Fields] OR strokepatienter[All Fields] OR strokepatients[All Fields] OR strokepharmacogenomics[All Fields] OR strokeplane[All Fields] OR strokeprevention[All Fields] OR strokeprofylax[All Fields] OR strokeprofylaxen[All Fields] OR strokeproject[All Fields] OR strokeprone[All Fields] OR stroker[All Fields] OR strokerehab[All Fields] OR strokerehabilitering[All Fields] OR strokerisk[All Fields] OR strokers[All Fields] OR strokerwin[All Fields] OR strokes[All Fields] OR strokes'[All Fields] OR strokes1[All Fields] OR strokesafe[All Fields] OR strokesand[All Fields] OR strokesektionen[All Fields] OR strokesfuture[All Fields] OR strokesich[All Fields] OR strokeskydd[All Fields] OR strokesmin[All Fields] OR strokestop[All Fields] OR strokestra[All Fields] OR strokestudygz[All Fields] OR strokethree[All Fields] OR stroketool[All Fields] OR stroketrials[All Fields] OR strokeun[All Fields] OR strokeunit[All Fields] OR strokevan[All Fields] OR strokevard[All Fields] OR strokevarden[All Fields] OR strokevia[All Fields] OR strokevision[All Fields] OR strokevolume[All Fields] OR strokevolumedon[All Fields] OR strokevolumes[All Fields] OR strokewidth[All Fields] OR strokework[All Fields] OR strokezero[All Fields]) OR (mortality[All Fields] OR mortality'[All Fields] OR mortality''[All Fields] OR mortality's[All Fields] OR mortality,[All Fields] OR mortality1[All Fields] OR mortality12[All Fields] OR mortality19[All Fields] OR mortality1965[All Fields] OR mortality2[All Fields] OR mortalityabc[All Fields] OR mortalityagainst[All Fields] OR mortalityall[All Fields] OR mortalityand[All Fields] OR mortalityat[All Fields] OR mortalitydagger[All Fields] OR mortalityfor[All Fields] OR mortalityhf[All Fields] OR mortalityin[All Fields] OR mortalityinterval[All Fields] OR mortalityinthe[All Fields] OR mortalitynrmand[All Fields] OR mortalityof[All Fields] OR mortalityon[All Fields] OR mortalitypredictors[All Fields] OR mortalityrate[All Fields] OR mortalityrates[All Fields] OR mortalityrelated[All Fields] OR mortalityresearch[All Fields] OR mortalitysahsubarachnoid[All Fields] OR mortalitystudy[All Fields] OR mortalitysuggests[All Fields] OR mortalitythat[All Fields] OR mortalitythree[All Fields] OR mortalitytrm[All Fields] OR mortalitytrmin[All Fields] OR mortalitywas[All Fields] OR mortalitywith[All Fields] OR mortalityworldwide[All Fields] OR mortalityyy[All Fields]) OR (cardiovascular disease[All Fields] OR cardiovascular disease's[All Fields] OR cardiovascular disease,[All Fields] OR cardiovascular diseased[All Fields] OR cardiovascular diseases[All Fields])) AND (Clinical Trial[ptyp] AND ("2014/01/01"[PDAT] : "2019/03/01"[PDAT]) AND "humans"[MeSH Terms])

Search string for reduced dietary fat, modified dietary fat or reduced saturated fat (Results = 10)	((reduced fat[All Fields] OR reduced fatalities[All Fields] OR reduced fatality[All Fields] OR reduced fatigability[All Fields] OR reduced fatiguability[All Fields] OR reduced fatigue[All Fields] OR reduced fatness[All Fields]) OR (modified fat[All Fields] OR modified fats[All Fields])) AND ((myocardial infarction[All Fields] OR myocardial infarction,[All Fields] OR myocardial infarctionl[All Fields] OR myocardial infarctions[All Fields]) OR (stroke[All Fields] OR stroke'[All Fields] OR stroke''[All Fields] OR stroke's[All Fields] OR stroke,[All Fields] OR stroke119[All Fields] OR stroke123[All Fields] OR stroke2[All Fields] OR stroke2000[All Fields] OR stroke2010[All Fields] OR stroke34[All Fields] OR stroke4carers[All Fields] OR stroke`s[All Fields] OR strokea[All Fields] OR strokeaetiology[All Fields] OR strokeaha[All Fields] OR strokeaha118020087[All Fields] OR strokeaha118020840[All Fields] OR strokeaha118021381[All Fields] OR strokeaha118021407[All Fields] OR strokeaha118021453[All Fields] OR strokeaha118021598[All Fields] OR strokeaha118021798[All Fields] OR strokeaha118022088[All Fields] OR strokeaha118022239[All Fields] OR strokeaha118022249[All Fields] OR strokeaha118022315[All Fields] OR strokeaha118022332[All Fields] OR strokeaha118022404[All Fields] OR strokeaha118022406[All Fields] OR strokeaha118022423[All Fields] OR strokeaha118022454[All Fields] OR strokeaha118022516[All Fields] OR strokeaha118022563[All Fields] OR strokeaha118022644[All Fields] OR strokeaha118022687[All Fields] OR strokeaha118022691[All Fields] OR strokeaha118022745[All Fields] OR strokeaha118022913[All Fields] OR strokeaha118022923[All Fields] OR strokeaha118023006[All Fields] OR strokeaha118023058[All Fields] OR strokeaha118023060[All Fields] OR strokeaha118023079[All Fields] OR strokeaha118023084[All Fields] OR strokeaha118023088[All Fields] OR strokeaha118023093[All Fields] OR strokeaha118023385[All Fields] OR strokeaha118023456[All Fields] OR strokeaha118023457[All Fields] OR strokeaha118023465[All Fields] OR strokeaha118023482[All Fields] OR strokeaha118023506[All Fields] OR strokeaha118023527[All Fields] OR strokeaha118023573[All Fields] OR strokeaha118023640[All Fields] OR strokeaha118023696[All Fields] OR strokeaha118023701[All Fields] OR strokeaha118023702[All Fields] OR strokeaha118023712[All Fields] OR strokeaha118023724[All Fields] OR strokeaha118023744[All Fields] OR strokeaha118023749[All Fields] OR strokeaha118023789[All Fields] OR strokeaha118023790[All Fields] OR strokeaha118023830[All Fields] OR strokeaha118023850[All Fields] OR strokeaha118023866[All Fields] OR strokeaha118023953[All Fields] OR strokeaha118023955[All Fields] OR strokeaha118023990[All Fields] OR strokeaha118024028[All Fields] OR strokeaha118024134[All Fields] OR strokeaha118024232[All Fields] OR strokeaha118024442[All Fields] OR strokeand[All Fields] OR strokecarecontents[All Fields] OR strokecenter[All Fields] OR strokecentre[All Fields] OR strokechecklist[All Fields] OR strokeclose[All Fields] OR strokect[All Fields] OR strokectacomputed[All Fields] OR strokectcomputed[All Fields] OR strokectomy[All Fields] OR stroked[All Fields] OR strokedepartment[All Fields] OR strokedepressive[All Fields] OR strokedge[All Fields] OR strokediagnostik[All Fields] OR strokedoc[All Fields] OR strokedrabbade[All Fields] OR strokeearly[All Fields] OR strokeed[All Fields] OR strokeelicited[All Fields] OR strokeenh[All Fields] OR strokeenheten[All Fields] OR strokefall[All Fields] OR strokefobrebyggande[All Fields] OR strokefoundation[All Fields] OR strokefree[All Fields] OR strokefrom[All Fields] OR strokehip[All Fields] OR strokein[All

	Fields] OR strokeinduced[All Fields] OR strokeintracerebral[All Fields] OR strokelets[All Fields] OR strokelike[All Fields] OR strokelink[All Fields] OR strokelocated[All Fields] OR strokemerci[All Fields] OR strokemethods[All Fields] OR strokemobile[All Fields] OR stroken[All Fields] OR strokenational[All Fields] OR strokenet[All Fields] OR strokengine[All Fields] OR strokengine's[All Fields] OR strokenomics[All Fields] OR strokenomics'[All Fields] OR strokepatienter[All Fields] OR strokepatients[All Fields] OR strokepharmacogenomics[All Fields] OR strokeplane[All Fields] OR strokeprevention[All Fields] OR strokeprofylax[All Fields] OR strokeprofylaxen[All Fields] OR strokeproject[All Fields] OR strokeprone[All Fields] OR stroker[All Fields] OR strokerehab[All Fields] OR strokerehabilitering[All Fields] OR strokerisk[All Fields] OR strokers[All Fields] OR strokerwin[All Fields] OR strokes[All Fields] OR strokes'[All Fields] OR strokes1[All Fields] OR strokesafe[All Fields] OR strokesand[All Fields] OR strokesektionen[All Fields] OR strokesfuture[All Fields] OR strokesich[All Fields] OR strokeskydd[All Fields] OR strokesmin[All Fields] OR strokestop[All Fields] OR strokestra[All Fields] OR strokestudygz[All Fields] OR strokethree[All Fields] OR stroketool[All Fields] OR stroketrials[All Fields] OR strokeun[All Fields] OR strokeunit[All Fields] OR strokevan[All Fields] OR strokevard[All Fields] OR strokevarden[All Fields] OR strokevia[All Fields] OR strokevision[All Fields] OR strokevolume[All Fields] OR strokevolumedon[All Fields] OR strokevolumes[All Fields] OR strokewidth[All Fields] OR strokework[All Fields] OR strokezero[All Fields]) OR (mortality[All Fields] OR mortality'[All Fields] OR mortality''[All Fields] OR mortality's[All Fields] OR mortality,[All Fields] OR mortality1[All Fields] OR mortality12[All Fields] OR mortality19[All Fields] OR mortality1965[All Fields] OR mortality2[All Fields] OR mortalityabc[All Fields] OR mortalityagainst[All Fields] OR mortalityall[All Fields] OR mortalityand[All Fields] OR mortalityat[All Fields] OR mortalitydagger[All Fields] OR mortalityfor[All Fields] OR mortalityhf[All Fields] OR mortalityin[All Fields] OR mortalityinterval[All Fields] OR mortalityinthe[All Fields] OR mortalitynrmand[All Fields] OR mortalityof[All Fields] OR mortalityon[All Fields] OR mortalitypredictors[All Fields] OR mortalityrate[All Fields] OR mortalityrates[All Fields] OR mortalityrelated[All Fields] OR mortalityresearch[All Fields] OR mortalitysahsubarachnoid[All Fields] OR mortalitystudy[All Fields] OR mortalitysuggests[All Fields] OR mortalitythat[All Fields] OR mortalitythree[All Fields] OR mortalitytrm[All Fields] OR mortalitytrmin[All Fields] OR mortalitywas[All Fields] OR mortalitywith[All Fields] OR mortalityworldwide[All Fields] OR mortalityyy[All Fields]) OR (cardiovascular disease[All Fields] OR cardiovascular disease's[All Fields] OR cardiovascular disease,[All Fields] OR cardiovascular diseased[All Fields] OR cardiovascular diseases[All Fields])) AND (Clinical Trial[ptyp] AND ("2014/01/01"[PDAT] : "2019/03/01"[PDAT]) AND "humans"[MeSH Terms]

Supplement Table 2. Ongoing Relevant Randomized Controlled Trials Identified Using ClinicalTrials.gov

Nutritional supplements			
Intervention	**Title [NCT number]**	**Condition**	**Completion date**
Vitamin K	Effect of Vitamin K2 (MK7) on cardiovascular and Bone Disease in Dialysis Patients [NCT02976246]	Vitamin K Supplementation; EndStage Renal Disease; Cardiovascular Disease; Bone Disease	August 2020
Antioxidant	Combined Antioxidant Therapy on Oxidative Stress, Mitochondrial Dysfunction Markers in Diabetic Retinopathy [NCT03702374]	Diabetic Retinopathy	November 2020
Sodium Selenite	SodiUm SeleniTe Adminstration IN Cardiac Surgery (SUSTAIN CSX®-Trial) [NCT02002247]	Heart Disease	June 2020
Vitamin E	Vitamin E and N-acetylcysteine for Preventing Contrast-Induced Acute Kidney Injury After Coronary Artery Catheterization [NCT03755700]	Coronary Artery Disease; Coronary Artery Angiography; Coronary Catheterization	December 2019
Multivitamins	Cocoa supplement and outcome study [NCT02422745]	Cardiovascular Disease; Cancer	October 2020
	The Effect of Multivitamin Supplement in Adult Femlaes [NCT03828097]	Healthy	June 2019
	Trial to Assess Chelation Therapy 2 [NCT02733185]	Diabetes; Myocardial Infarction	December 2021
Selenium	Selenium Treatment and Chagasic Cardiopathy (STCC) [NCT00875173]	Chagas Disease	December 2020
Tocotrienol	Stroke and Tocotrienol : Unique Role in Neuroprotection [NCT02263924]	Ischemic Stroke	December 2018
Tocotrienols	Safety and Efficacy of Tocotrienols in Post-CABG Atrial Fibrillation [NCT03807037]	Atrial Fibrillation	January 30, 2020
Menaquinone-7 (Vitamin K2)	The effect of ViatminK2 supplemntation on the progression of coronary artery calcification [NCT01002157]	Coronary Artery Disease	October 2019
Menaquinone-7	A Randomized, Placebo-Controlled, Double Blind Trial to Investigate Whether Vitamin K2 can Influence Arterial Calcification in Patients with Type 2 Diabetes [NCT02839044]	Arterial Calcification Diabetes Mellitus Type 2	December 2018
Vitamin D	Vitamin D, Cardiovascular Disease, and African Americans [NCT01655810]	Vitamin D Deficiency; Type 2 Diabetes Mellitus; Cardiovascular Disease	December 2018
	Effect of Vitamin D3 Supplementation on Cardiometabolic Risk [NCT02359214]	Cardiovascular Disease; Diabetes ; Bone Disease	December 2017

	Vitamin D and Omega-3 Trial (VITAL) [NCT01169259]	Cancer ; Cardiovascular Disease	November 2020
	Vitamin D, Insulin Resistance, and Cardiovascular Disease [NCT00736632]	Vitamin D Deficiency; Insulin Resistance; Type 2 Diabetes Mellitus	December 2018
Vitamin D + fish oil/fish oil placebo	Impact of Vitamin D Supplementation on Cardiac Structure and Function [NCT01630213]	Cardiovascular Disease	December 2020
Vitamin D and fish oil	Intervention With Vitamin D and Omega-3 Supplements and Incident Heart Failure [NCT02271230]	Heart Failure	June 2019
n-3 LC PUFA	Outcome Study of Assess STatin Resideual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia [NCT02104817]	Eligible Men or Women Considered High Risk for Atherosclerotic Cardiovascular Disease	October 2019
	ASCEND : A Study of Cardiovascular events in Diabetes	Diabetes Mellitus	July 2037
Dietary interventions			
Blueberry Powder	Blueberries for Improving Vascular Endothelial Function in Postmenopausal Women With Elevated Blood Pressure [NCT03370991]	Menopause; Hypertension; Endothelial dysfunction	December 2019
Mediterranean diet	CORonary Diet Intervention With Olive Oil and Cardiovascular PREVention (CORDIOPREV) [NCT00924937]	Myocardial Infarction; Unstable Angina; Malignancy; Cognitive impairment	September 2019
	The Mediterranean Full-Fat Dairy Study [NCT02781675]	Cardiovascular disease; Dyslipidemia; Inflammation	December 2018
Modified Citrus Pectin	Galactein-3 Blockade in Patients With High Blood Pressure [NCT01960946]	Hypertension	October 2020
Salt	SODIUM HF : Study of Dietary Intervention Under 100 MMOL in Heart Failure [NCT02012179]	Heart Failure	December 2023
Plant-Based Diet	Plant-Based, American Heart Assoc. Or Mediterranean Diets n 9-18 yo With BMI >95%, Cholesterol >169 and Their Parents [NCT02857543]	Obesity; Hypercholesterolemia; Cardiovascular disease	December 2019
Almonds	The Impact of Almond Nut Consumption on Markers of CVD & Metabolic Health [NCT02907684]	Cardiovascular disease	April 30, 2019
Vegetarian Diet followed by meat Diet or vice versa	Vegetarian Diet in Patients With Ischemic Heart Disease [NCT02942628]	Ischemic Heart Disease	March 2019

Dietary Supplement : grape seed extract	The Effect of Grape Seed Extract on Blood Pressure in People With Pre-Hypertension [NCT00979732]	Hypertension	October 15, 2019
R-Alpha Lipoic Acid	The Role of R-Alpha Lipoic Acid in the Treatment of Atherosclerotic Vascular Disease [NCT00764270]	Atherosclerosis	December 2018
	Lipoic Acid and Prevention of Heart Disease [NCT00765310]	Atherosclerosis	December 2018
L-carnitine capsules	Carnitine for the Treatment of Atherosclerosis [NCT02117661]	Metabolic Syndrome	May 2019
Salmon-Polar Lipids	In Vitro And Ex Vivi Anti-Inflammatory Acitivities of Salmon Polar Lipids [NCT03603769]	Cardiovascular Disease	November 2018
Whole Eggs	Cardioprotective Activities of Whole Egges on Vascular Endothelial Function in Prediabetic Adults [NCT02364570]	Prediabetes; Cardiovascular Disease	December 2017
Search terms used : Multivitamins; minerals; Diet; Antioxidants; β-carotene; vitamin B-complex; multivitamins; selenium; vitamin A; vitamin B3/Niacin; vitamin B6; vitamin C; vitamin E; vitamin D; calcium + vitamin D; calcium; folic acid; iron; Omega 3 Fatty Acid; Omega 6 Fatty Acid; Salt; Fat. Eligibility Criteria : [Adult (18-64)] and [old adult (65+)] and study type; [interventional]			

Supplement Table 3. Randomized Controlled Trials Included in Analyses

Study (reference)	Supplement exposure	Participants
Brohult et al., 1973 (10)	Vitamin D	50
CDPRG 1975(11)	Vitamin B3	3908
Gillilan et al., 1977 (12)	Vitamin E	52
Inkovaara et al., 1983(13)	Vitamin D	87
	Calcium + Vitamin D	88
Corless et al., 1985 (14)	Vitamin D_2	82
Aloia et al., 1988(15)	Vitamin D	27
Korpela et al., 1989(16)	Selenium	81
McKeown-Eyssen et al., 1988 (17)	vitamins C and E	185
Ott et al., 1989(18)	Vitamin D	86
Gallagher et al., 1990 (19)	Vitamin D	50
Grady et al., 1991 (20)	Vitamin D_3	98
Chapuy et al., 1992 (21)	Calcium + Vitamin D_3	3270
Li et al., 1993 – NIT2(22)	Multivitamins	3318
Bogden et al., 1994 (23)	Multivitamins	65
de la Maza et al., 1995 (24)	Vitamin E	74
Hamdy et al., 1995 (25)	Vitamin D	176
Ooms et al., 1995 (26)	Vitamin D_3	348
Pike et al., 1995 (27)	Multivitamins	47
Steiner et al., 1995 (28)	α- tocopherol	100
Greenberg et al., 1996 – SCPS (29)	β-carotene	1805
Hennekens et al., 1996-PHS (30)	β-carotene	22071
Lips et al., 1996 (31)	Vitamin D_3	2578
Omenn et al., 1996 – CARET (32)	β-carotene	18314
Stephens et al., 1996 – CHAOS (33)	Vitamin E	2002
Dawson-Hughes et al., 1997 (34)	Calcium + Vitamin D_3	389
Girodon et al., 1997 (35)	Antioxidants: zinc sulfate, selenite, Vitamin C, β-carotene α-tocopherol	41
Moon et al., 1997 – SKICAP AK (36)	Retinol	2297
Sano et al., 1997 – ADCS 1 (37)	Vitamin E	169

Sato et al., 1997 (38)	Vitamin D	84
Baeksgaard et al., 1998 (39)	Calcium + Vitamin D	160
Shoulson et al., 1998 – DATATOP (40)	Vitamin E	800
Virtamo et al., 1998 – ATBC (41)	Vitamin E	13669
Baron et al., 1999 – CPPS (42)	Calcium	930
Hoffman et al., 1999 (43)	Vitamin E	39
Girodon et al., 1999 – MIN.VIT.AOX (44)	Antioxidants: Zinc, Selenium, Vitamin C, β-carotene, α-tocopherol)	363
GISSI – Prevenzione Investigators 1999 (45)	Vitamin E and n-3 LC PUFA	11324
Green et al., 1999 – NSCPT (46)	β-carotene	1621
Komulainen et al., 1999 – OSTPRE (47)	Vitamin D	227
	Calcium + Vitamin D	231
Krieg et al., 1999 (48)	Calcium + Vitamin D	248
Sato et al., 1999 (49)	Vitamin D	86
Boaz et al., 2000 – SPACE (50)	Vitamin E	196
Correa et al., 2000 (51)	Vitamin C	247
	β-carotene	234
	Antioxidants: Vitamin C and β-carotene	238
Frazao et al., 2000 (52)	Vitamin D	138
Lee et al., 1999 – WHS (53)	β-carotene	39876
Leppälä et al., 2000 – ATBC (54)	Antioxidants: Vitamin E, β-carotene	14271
	β-carotene	28519
Jacobson et al., 2000 (55)	Antioxidants: vitamin C, a-tocopherol, β-carotene	112
Salonen et al., 2000 – ASAP (56)	Vitamin E	260
	Vitamin C	260
AREDS Research Group 2001 (57)	Antioxidants: Vitamin C, Vitamin E, β-carotene, zinc	4629
Brown et al., 2001 – HATS (58)	Antioxidants: Vitamin E + Vitamin C + β-carotene + selenium	80
de Gaetano et al., 2001 – PPP (59)	α-tocopherol	4495
Desnuelle et al., 2001 – ALSRT (60)	α-tocopherol	288
de Waart et al., 2001 (61)	Vitamin E	218
Gallagher et al., 2001 – STOP IT (62)	Vitamin D	246
You et al., 2001 – SIT (63)	Antioxidants: Vitamin C + Vitamin E + β-carotene + selenium	3411
Baker et al., 2002 (64)	Folic acid	1882
Chapuy et al., 2002 – Decalyos II (65)	Calcium + Vitamin D_3	583

Chylack et al., 2002 – REACT (66)	Antioxidants: β-carotene, vitamin C, vitamin E	297
Graat et al., 2002 (67)	Vitamin E	317
	Multivitamin	316
Hodis et al., 2002 – VEAPS (68)	Vitamin E	353
HPS Collaborative Group 2002 (69)	Antioxidants: Vitamin E + Vitamin C + β-carotene	20536
Meyer et al., 2002 (70)	Vitamin D	1144
Schnyder et al., 2002 – The Swiss Heart Study (71)	Vitamin B-complex (folic acid, vitamin B_{12}, vitamin B_6)	553
Waters et al., 2002 – WAVE (72)	Antioxidants: vitamin E + Vitamin C	213
Wluka et al., 2002 (73)	Vitamin E	136
Collins et al., 2003 (74)	Vitamin E	52
Cooper et al., 2003 (75)	Vitamin D	187
Liem et al., 2003 (76)	Folic acid	593
Righetti et al., 2003 (77)	Folic acid	81
Trivedi et al., 2003 (78)	Vitamin D	2686
Virtamo et al., 2003 – ATBC (79)	β-carotene	14569
	Vitamin E	14573
Dukas et al., 2004 (80)	Vitamin D	378
Harwood et al., 2004 – NoNOF (81)	Vitamin D	75
	Calcium + Vitamin D_3	76
Coburn et al., 2004 (82)	Vitamin D	55
Lange et al., 2004 (83)	Vitamin B-complex (folic acid, vitamin B_{12}, vitamin B_6)	636
Larsen et al., 2004 (84)	Calcium + Vitamin D_3	9605
Liem et al., 2004 (85)	Folic acid	283
Taylor et al., 2004 – ARBITER 2 (86)	Vitamin B3 (niacin)	167
Tornwall et al., 2004 – ATBC (87)	Antioxidants: α-tocopherol, β-carotene	13630
	β-carotene	13670
Manuel-Y-Keenoy et al., 2004 – DATOR (88)	α-tocopherol	24
McNeil et al., 2004 – VECAT (89)	Vitamin E	1193
Meier et al., 2004 (90)	Calcium + Vitamin D_3	55
Meydani et al., 2004 (91)	Vitamin	617
Aloia et al., 2005 (92)	Vitamin D_3	208

Avenell et al., 2005 – MAVIS (93)	Multivitamin	910
Brazier et al., 2005 (94)	Calcium + Vitamin D_3	192
Flicker et al., 2005 (95)	Vitamin D	625
Graf et al., 2005 (96)	Vitamin E	160
Grant et al., 2005 – RECORD (97)	Calcium + Vitamin D_3	2638
	Calcium only	2241
	Vitamin D only	5292
Lee et al., 2005 –WHS (98)	Vitamin E	39876
Limburg et al., 2005 (99)	Selenomethionine	180
Lonn et al., 2005 – HOPE and HOPE-TOO (100)	Vitamin E	9541
Mooney et al., 2005 (101)	Vitamin C and E	284
Petersen et al, 2005 – ADCS 2 (102)	Vitamin E	516
Porthouse et al., 2005 (103)	Calcium+Vitamin D	3314
Potena et al., 2005 (104)	Folic acid	51
Sato et al., 2005 (105)	Vitamin D	96
Bairati et al., 2006 (106)	α –tocopherol	384
Bonaa et al., 2006 – NORVIT (107)	Vitamin B6	1877
	B-complex	1880
Coyne et al., 2006 (108)	Vitamin D	220
Daly et al., 2006 (109)	Calcium+Vitamin D	167
Law et al., 2006 (110)	Vitamin D	3717
Lonn et al., 2006 – HOPE-TOO (111)	Vitamin B-complex (folic acid, vitamin B_6, vitamin B_{12})	5522
Magliano et al., 2006 – MAVET (112)	Vitamin E	409
Schleithoff et al., 2006 (113)	Calcium + Vitamin D_3	123
Stranges et al., 2006 – NPC (114)	Selenium	1004
Zoungas et al., 2006 – ASFAST (115)	Folic acid	315
Bolton-Smith et al., 2007 (116)	Calcium/Vitamin D	123
CLIPS Group 2007 (117)	vitams: vitamin E + vitamin C + β-carotene	366
Cole et al., 2007 – AFPPS (118)	Folic acid	1021
Cook et al., 2007 – WACS (119)	β-carotene	8171
	Vitamin C	8171
	Vitamin E	8171

	Antioxidants: Vitamin C, Vitamin E and β-carotene	2042
Durga et al., 2007 – FACIT (120)	Folic acid	818
Jamison et al., 2007 – HOST (121)	Vitamin B complex	2056
Lappe et al., 2007 (122)	Calcium+Vitamin D	734
Liu et al., 2007 (123)	Multivitamin	748
Lyons et al., 2007 (124)	Vitamin D	3440
Plummer et al., 2007 (125)	Antioxidants: vitamin C + vitamin E + β-carotene	1980
Smith et al., 2007 (126)	Vitamin D	9440
Vianna et al., 2007 (118)	Folic acid	186
Albert et al., 2008 – WAFACS (119)	Vitamin B-complex (folic acid, vitamin B_6, and vitamin B_{12})	5442
Bjorkman et al., 2008 (127)	Vitamin D	141
Bolland et al., 2008 (128)	Calcium	1471
CTNS 2008 (129)	Multivitamins	1020
Ebbing et al., 2008-WENBIT (130)	B-complex	1552
	Vitamin B6	1552
Guyton et al., 2008 (131)	Vitamin B3/ niacin	942
Logan et al., 2008 – UK CAP (132)	Foliac acid	939
Milman et al., 2008 (133)	Vitamin E	1434
Prince et al., 2008 (134)	Vitamin D with or without calcium	302
Reid et al., 2008 (135)	Calcium	215
Sesso et al., 2008 – PHS II (136)	Vitamin E with or without Vitamin C	7312
	Antioxidants (vitamin E and vitamin C)	7309
	Vitamin C	7326
Zhu et al., 2008 – CAIFOS (137)	Calcium + Vitamin D	80
Anker et al., 2009 – FAIR-HF (138)	Iron	459
Hodis et al., 2009 – BVAIT (139)	Vitamin B-complex (folic acid + vitamin B12 + vitamin B6)	506
Imasa et al., 2009 (140)	Vitamin B-complex (folic acid, vitamin B12, and vitamin B6)	243
LaCroix et al., 2009 – WHI (141)	Calcium+Vitamin D	36282
Lippman et al., 2009 – SELECT (142)	Selenium	17766
	Vitamin E	17773
	Selenium and Vitamin E	17814
Saposnik et al., 2009 – HOPE 2 (143)	Vitamin B-complex (folic acid, vitamin B12, and vitamin B6)	5522

Sang et al., 2009 (144)	Vitamin B13/Niacin	108
Wu et al., 2009 – NHS/HPFS(145)	Folic acid	672
Armitage et al., 2010 – SEARCH (146)	Vitamin B-complex (folic acid, vitamin B12)	12064
Chailurkit et al., 2010 (147)	Calcium	397
de Zeeuw et al., 2010 – VITAL (148)	Vitamin D	188
Galan et al., 2010 – SU.FOL.OM3 (149)	Vitamin B-complex (folic acid, vitamin B12, and vitamin B6)	2501
Heinz et al., 2010 (150)	Vitamin B-complex (folic acid, vitamin B12, and vitamin B6)	650
Hercberg et al., 2010 – SU.VI.MAX (151)	Antioxidants: (Vitamin C + vitamin E + β-carotene + selenium + zinc	12741
House et al., 2010 – DIVINe (152)	Vitamin B-complex (folic acid, vitamin B12, and vitamin B6)	238
Janssen et al., 2010 (153)	Vitamin D	70
Salovaara et al., 2010 – OSTRE-FPS (154)	Vitamin D + Calcium	3195
Sanders et al., 2010 – Vital D (155)	Vitamin D	2258
Sanyal et al., 2010 – PIVENS (156)	Vitamin E	167
VITATOPS Trial Study Group 2010 (157)	Vitamin B-complex (folic acid, vitamin B12, and vitamin B6)	8164
Boden et al., 2011 – AIM HIGH (158)	Vitamin B3/Niacin	3414
Cherniack et al., 2011 (159)	Vitamin D	46
Grimnes et al., 2011 (160)	Vitamin D	104
Lewis et al., 2011 – CAIFOS (161)	Calcium	1460
Gallagher et al., 2012 – VIDOS (162)	Vitamin D_3	41
Marshall et al., 2011 (163)	Selenium	423
Alvarez et al., 2012 (164)	Vitamin D_3	48
Glendenning et al., 2012 (165)	Vitamin D	686
Lehouck et al., 2012 (166)	Vitamin D	182
Ma et al., 2012 – SIT (167)	Antioxidants (Vitamin C + Vitamin E + β-carotene + selenium)	3411
Punthakee et al., 2012 – TIDE (168)	Vitamin D	1221
Sesso et al., 2012 – PHS II (169)	Multivitamin	14641
Delanaye et al., 2013 (170)	Vitamin D	43
Hewitt et al., 2013 (171)	Vitamin D	60
Lamas et al., 2013 – TACT (172)	Multivitamins (28-component mixture)	1708
Manning et al., 2013 (173)	Vitamin E	76
Prentice et al., 2013 –WHI CaD (174)	Calcium + Vitamin D_3	15302
Witham et al., 2013 – VitDISH (175)	Vitamin D	159
Witham et al., 2013 (176)	Vitamin D3	75

HPS2-THRIVE Collaborative Group 2014 (177)	Vitamin B3/Niacin	25673
Wang et al., 2014 – OPERA (178)	Vitamin D	60
Van Wijngaarden et al., 2014 – B-PROOF (179)	Vitamin B-complex (vitamin B_{12} + folic acid)	3027
Wang et al., 2014 – PHS II (180)	Vitamin E	7312
	Vitamin C	7326
	Antioxidants (Vitamin E and C)	7309
Huo et al., 2015 – CSPPT (181)	Folic acid	20702
Ponikowski et al., 2015 – CONFIRM-HF (182)	Iron	301
Wang et al., 2015 (183)	Folic acid, vitamin B6, 10 µg vitamin B12	390
Van Dijk et al., 2015 – B-PROOF (184)	Vitamin B-complex (folic acid, vitamin B12, and vitamin B6)	3027
Gupta et al., 2016 (185)	Calcium + Vitamin D	53
Lappe et al., 2017 (186)	Calcium + Vitamin D	2303
Brox et al., 2001(187)	n-3 LC PUFA	80
EPIC-1,2008(188)	n-3 LC PUFA	374
EPIC-2, 2008 (188)	n-3 LC PUFA	379
Nye et al., 1990 (189)	n-3 LC PUFA	73
FOSTAR, 2016(190)	n-3 LC PUFA and n-3 ALA PUFA	202
HARP, 1995(191)	n-3 LC PUFA	59
AFFORD, 2013(192)	n-3 LC PUFA vs n-6 PUFA	337
Berson et al., 2004 (193)	n-3 LC PUFA vs n-6 PUFA	208
Nutristroke et al., 2009 (194)	n-3 LC PUFA	72
Zhang et al., 2017 (195)	n-3 LC PUFA vs n-6 PUFA	240
Bates et al., 1989(196)	n-3 LC PUFA	312
Derosa et al., 2016(197)	n-3 LC PUFA	258
Kumar et al., 2013(198)	n-3 LC PUFA	78
Baldassarre et al., 2006 (199)	n-3 LC PUFA	64
THIS DIET, 2008 (200)	n-3 LC PUFA	101
SCIMO, 1999(201)	n-3 LC PUFA	223

Shinto et al., 2014(202)	n-3 LC PUFA	26
DIPP, 2015(203)	n-3 LC PUFA and n-3 ALA PUFA	205
Doi et al., 2014(204)	n-3 LC PUFA	238
NAT2, 2013(205)	n-3 LC PUFA	263
FORWARD, 2013 (206)	n-3 LC PUFA	586
Nodari et al., 2011(207)	n-3 LC PUFA	188
Raitt et al., 2005(208)	n-3 LC PUFA	200
Ozaydin et al., 2011 (209)	n-3 LC PUFA	47
DISAF, 2003(210)	n-3 LC PUFA	407
Shot et al, 1996(211)	n-3 LC PUFA	610
SOFA, 2006(212)	n-3 LC PUFA and n-6 PUFA	546
OPAL, 2010 (213)	n-3 LC PUFA	748
OFAMI, 2001(214)	n-3 LC PUFA	300
ADCS., 2010(215)	n-3 LC PUFA	402
FAAT, 2005(216)	n-3 LC PUFA	402
DO IT, 2010(217)	n-3 LC PUFA	563
MAPT, 2017 (218)	n-3 LC PUFA	1652
SU.FOL.OM3, 2010 (219)	n-3 LC PUFA	2501
OMEGA, 2009(220)	n-3 LC PUFA	54
DART, 1989(221)	n-3 LC PUFA/ Reduced saturated fat/n-6 PUFA	2033
AlphaOmega - EPA+DHA 2010, (222)	n-3 LC PUFA	4837
ORL, 2013 (223)	n-3 LC PUFA	336
AREDS2, 2014(224)	n-3 LC PUFA	4203
EPOCH, 2014 (225, 226)	n-3 LC PUFA	391
Proudman et al. 2015 (227, 228)	n-3 LC PUFA vs n-6 PUFA	122
MAPT-PLUS, 2017 (229)	n-3 LC PUFA	1680

EPE-A, 2014 (230)	n-3 LC PUFA	174
DART-2,2003 (231)	n-3 LC PUFA/Mediterranean diet	3114
JELIS, 2007 (232)	n-3 LC PUFA	18645
Risk % Prevention, 2013 (233)	n-3 LC PUFA	12505
ORIGIN, 2012 (234)	n-3 LC PUFA	12506
GISSI-HF, 2008 (235)	n-3 LC PUFA	6975
Bates et al., 1978 (236)	n-6 PUFA	58
AlphaOmega-ALA 2010 (222, 237-239)	n-3 ALA	2433
FLAX-PAD 2013 (240)	n-3 ALA	110
MARGARIN, 2002 (241)	n-3 ALA	282
Norwegian study, 1968 (242)	n-3 ALA	13406
WAHA, 2016(243)	n-3 ALA	708
Black et al., 1994 (244)	Reduced dietary fat (lower n-6 PUFA + total PUFA)/ Reduced saturated fat	133
MCIIIMURRAY et al., 1987(245)	n-6 PUFA	49
MRC, 1968(246)	n-6 PUFA/ Modiefied fat/ Reduced saturated fat	393
NDHS FERIBAULT, 1968(247)	n-6 PUFA/ Modified dietary fat	224
ROSE CORN OIL , 1965(248)	n-6 PUFA/ Reduced saturated fat	54
SYDNEY DIET HEART, 1978(249)	n-6 PUFA/ Reduced saturated fat/ Modified dietary fat	458
VETERANS ADMIN, 1969(250)	n-6 PUFA/ Reduced saturated fat/ Modified dietary fat	846
Vijay Kumar et al., 2014 (251)	n-6 PUFA	200
GLAMT, 1993 (252)	n-6 PUFA	111
Houtsmuller et al. 1979 (253)	n-6 PUFA	102
Moy et al. 2001 (254)	Reduced dietary fat intake	235
Ley et al., 2004 (255)	Reduced dietary fat/Reduced dietary fat	176
OSLO DIET HEART, 1966 (256)	Reduced saturated fat/Modified dietary fat	412

STARS, 1992(257)	Reduced saturated fat	45
WHI WITHOUT CVD, 2006(258)	Reduced saturated fat/ Reduced dietary fat	48835
WINS, 2006 (259)	Reduced dietary fat	2437
Ball et al., 1965 (260)	Reduced dietary fat	252
POLYP PREVENTION., 1996(261)	Reduced dietary fat	2079
Bridges et al., 2001(262)	Reduced dietary fat	106
PREMIER,2003 (263)	Reduced dietary fat	537
DO IT 2006 (264)	Reduced dietary fat	487
WHEL., 2007 (265)	Reduced dietary fat	3088
Rose et al., 1965 (266)	Modified dietary fat	52
MINNESOTA CORON WOMEN/MEN., 1989(267)	Modified dietary fat	Women (4664), Men (4664)
Chang et al., 2006 (268)	Salt reduction	1981
CSSS., 2007(269)	Salt reduction	608
Kwok et al., 2012 (270)	Salt reduction	429
Morgan et al., 1978(271)	Salt reduction	67
TONE., 1998 (272)	Salt reduction	681
HPT., 1990(273)	Salt reduction	392
TOHP1., 1992 (274)	Salt reduction	744
TOHP2, 1997 (275)	Salt reduction	2382
PREDIMED, 2013 (276)	Mediterranean diet	7447
Ng et al., 2011(277)	Mediterranean diet	48
Singh et al.,(278)	Mediterranean diet	1000
de Lorgeril et al., 1994 (279)	Mediaterranean diet	605
CLAS, 1987 (280)	Vitamin B3/Niacin	188
Whitney et al., 2005 (281)	Vitamin B3/Niacin	143
VITAL, 2018 (282)	Vitamin D	25,871

VIDA, 2017 (283)	Vitamin D	5,108
*ONTARGET, 2008 (284)	Reduced salt	28757
* TRANSCEND, 2008 (285)	Reduced salt	
VITAL, 2018 (286)	n-3 LC PUFA	25,871
ASCEND, 2018 (287)	n-3 LC PUFA	15,480

* ONTARGET was a randomised, double-blind, parallel trial comparing the eff ects of ramipril (10 mg/day), telmisartan (80 mg/day), and combination therapy of ramipril (10 mg/day) and telmisartan (80 mg/day) in 25 620 patients, with vascular disease or high-risk patients with diabetes. TRANSCEND was a randomised controlled trial comparing telmisartan (80 mg/day) with placebo in 5926 participants who were intolerant to angiotensin converting enzyme inhibitors. For this analysis, we included 28 757 participants from individual patient meta-analysis ONTARGET and TRANSCEND by Mente et al.

Supplement Table 4. Methological Quality Assessment of Included Systematic Reviews and Meta-analyses

Author (Year)	Appropriate search criteria	Appropriate selection criteria	Method of pooling estimates	Assessment of risk of bias	Assessment of Publication bias	Assessment of heterogeinity
Jenkins D et al. (2018) (1)	Yes	Yes	Random effects	Yes	Yes	Yes
Riaz H et al. (2018) (2)	Yes	Yes	Random effects	Yes	Yes	Yes
Abdelhamid AS et al. (2018) (3)	Yes	Yes	Random effects/Fixed effects	Yes	Yes	Yes
Hooper L et al. (2018) (4)	Yes	Yes	Random effects/Fixed effects	Yes	Yes	Yes
Liyanage T et al. (2016) (5)	Yes	Yes	Fixed effects	Yes	No	No
Adler AJ et al. (2014) (6)	Yes	Yes	Fixed effects/Random effects	Yes	No	Yes
*Mente A et al. (2016) (7)	Yes	No	No	No	No	No
Hooper L et al. (2012) (8)	Yes	Yes	Random effects/Fixed effects	Yes	Yes	Yes
Hooper L et al. (2015) (9)	Yes	Yes	Random effects/Fixed effects	Yes	Yes	Yes

* Mente A et al. was individual level analysis of 4 studies.

Supplement Table 5 (a-x). GRADE Scale for Quality Assessment of Evidence

a. Vitamin E Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
32	randomised trials	not serious	not serious	very serious [a,b]	not serious [c]	none [d]	**RR 1.00** (0.97 to 1.03)	⊕⊕◯◯ LOW
Cardiovascular mortality								
11	randomised trials	not serious	not serious [e]	very serious [a]	serious [c]	none	**RR 0.95** (0.88 to 1.03)	⊕◯◯◯ VERY LOW
MI								
10	randomised trials	not serious	very serious [e]	very serious [a]	serious [c]	publication bias strongly suspected [d]	**RR 0.83** (0.65 to 1.05)	⊕◯◯◯ VERY LOW
Stroke								
11	randomised trials	not serious	not serious [e]	very serious [b]	very serious [c]	publication bias strongly suspected [d]	**RR 0.98** (0.87 to 1.10)	⊕◯◯◯ VERY LOW
CHD								
2	randomised trials	not serious	not serious [e]	very serious [a]	serious [c]	none	**RR 0.97** (0.90 to 1.05)	⊕◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

b. Vitamin C Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
4	randomised trials	not serious	not serious	not serious [a,b]	very serious [c]	none [d]	**RR 1.02** (0.94 to 1.11)	⊕⊕◯◯ LOW
Cardiovascular mortality								
2	randomised trials	not serious	not serious [e]	not serious [a]	very serious [c]	none	**RR 1.07** (0.87 to 1.33)	⊕⊕◯◯ LOW
MI								
2	randomised trials	not serious	not serious [e]	not serious [a]	very serious [c]	none	**RR 0.96** (0.32 to 2.89)	⊕⊕◯◯ LOW
Stroke								
2	randomised trials	not serious	not serious [e]	not serious [b]	very serious [c]	none	**RR 0.92** (0.35 to 2.40)	⊕⊕◯◯ LOW
CHD								
1	randomised trials	not serious	not serious [e]	not serious [a]	very serious [c]	none	**RR 1.04** (0.93 to 1.17)	⊕⊕◯◯ LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

c. Vitamin B-Complex Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
16	randomised trials	not serious	not serious	not serious [a,b]	serious [c]	none [d]	**RR 1.02** (0.97 to 1.07)	⨁⨁⨁◯ MODERATE
Cardiovascular mortality								
5	randomised trials	not serious	very serious [e]	not serious [a]	very serious [c]	none	**RR 1.00** (0.79 to 1.26)	⨁◯◯◯ VERY LOW
MI								
13	randomised trials	not serious	not serious [e]	not serious [a]	very serious [c]	none	**RR 1.00** (0.94 to 1.07)	⨁⨁◯◯ LOW
Stroke								
12	randomised trials	not serious	not serious [e]	not serious [b]	serious [c]	none	**RR 0.90** (0.80 to 1.01)	⨁⨁⨁◯ MODERATE
CHD								
5	randomised trials	not serious	not serious [e]	not serious [a]	very serious [c]	none	**RR 1.05** (0.90 to 1.23)	⨁⨁◯◯ LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

d. Vitamin B6 Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
2	randomised trials	not serious	not serious	not serious [a,b]	very serious [c]	none [d]	**RR 1.02** (0.59 to 1.76)	⨁⨁◯◯ LOW
MI								
2	randomised trials	not serious	not serious [e]	not serious [a]	very serious [c]	none	**RR 1.04** (0.59 to 1.82)	⨁⨁◯◯ LOW
Stroke								
2	randomised trials	not serious	not serious [e]	serious [b]	very serious [c]	none	**RR 0.92** (0.18 to 4.67)	⨁◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

e. Vitamin B3/Niacin Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
5	randomised trials	not serious	not serious	serious [a,b]	very serious [c]	none [d]	**RR 1.04** (0.94 to 1.16)	⊕◯◯◯ VERY LOW
Cardiovascular mortality								
4	randomised trials	not serious	not serious [e]	serious [a]	very serious [c]	none	**RR 0.95** (0.82 to 1.11)	⊕◯◯◯ VERY LOW
MI								
6	randomised trials	not serious	serious [e]	serious [a]	very serious [c]	none	**RR 0.89** (0.72 to 1.10)	⊕◯◯◯ VERY LOW
Stroke								
5	randomised trials	not serious	very serious [e]	serious [b]	very serious [c]	none	**RR 0.96** (0.56 to 1.66)	⊕◯◯◯ VERY LOW
CHD								
2	randomised trials	not serious	not serious [e]	serious [a]	very serious [c]	none	**RR 0.96** (0.87 to 1.06)	⊕◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

f. Vitamin A Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
1	randomised trials	not serious	not serious	not serious [a,b]	very serious [c]	none [d]	**RR 0.99** (0.56 to 1.72)	⨁⨁◯◯ LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

g. Selenium Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
4	randomised trials	not serious	not serious	very serious [a,b]	very serious [c]	none [d]	**RR 0.99** (0.89 to 1.10)	⊕◯◯◯ VERY LOW
Cardiovascular mortality								
3	randomised trials	not serious	serious [e]	very serious [a]	very serious [c]	none	**RR 0.92** (0.15 to 5.63)	⊕◯◯◯ VERY LOW
MI								
2	randomised trials	not serious	not serious [e]	very serious [a]	very serious [c]	none	**RR 0.93** (0.25 to 3.45)	⊕◯◯◯ VERY LOW
Stroke								
2	randomised trials	not serious	not serious [e]	very serious [b]	very serious [c]	none	**RR 0.89** (0.19 to 4.27)	⊕◯◯◯ VERY LOW
CHD								
1	randomised trials	not serious	not serious	not serious	very serious [c]	none	**RR 1.06** (0.76 to 1.48)	⊕⊕◯◯ LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

h. Multivitamins Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
10	randomised trials	not serious	not serious	not serious [a,b]	serious [c]	none [d]	**RR 0.95** (0.90 to 1.01)	⊕⊕⊕◯ MODERATE
Cardiovascular mortality								
3	randomised trials	not serious	not serious [e]	not serious [a]	very serious [c]	none	**RR 0.94** (0.74 to 1.19)	⊕⊕◯◯ LOW
MI								
3	randomised trials	not serious	not serious [e]	not serious [a]	very serious [c]	none	**RR 0.95** (0.82 to 1.09)	⊕⊕◯◯ LOW
Stroke								
2	randomised trials	not serious	very serious [e]	not serious	very serious [c]	none	**RR 0.86** (0.01 to 50.30)	⊕◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

i. Iron Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
2	randomised trials	not serious	not serious	not serious [a,b]	very serious [c]	none [d]	**RR 0.79** (0.16 to 3.85)	⨁⨁◯◯ LOW
Cardiovascular mortality								
2	randomised trials	not serious	not serious [e]	not serious [a]	very serious [c]	none	**RR 0.80** (0.03 to 20.50)	⨁⨁◯◯ LOW
MI								
1	randomised trials	not serious	not serious [e]	not serious [a]	very serious [c]	none	**RR 0.34** (0.06 to 2.01)	⨁⨁◯◯ LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

j. Folic Acid Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
10	randomised trials	not serious	not serious	serious [a,b]	very serious [c]	none	**RR 0.85** (0.65 to 1.10)	⨁◯◯◯ VERY LOW
Cardiovascular mortality								
5	randomised trials	not serious	not serious [d]	serious [a]	very serious [c]	none	**RR 0.89** (0.68 to 1.17)	⨁◯◯◯ VERY LOW
MI								
6	randomised trials	not serious	not serious [d]	serious [a]	very serious [c]	none	**RR 1.22** (0.66 to 2.24)	⨁◯◯◯ VERY LOW
Stroke								
7	randomised trials	not serious	not serious	serious [a]	serious [c]	none	**RR 0.80** (0.67 to 0.96)	⨁⨁◯◯ LOW
CHD								
2	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	**RR 1.47** (0.10 to 22.50)	⨁◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

k. Calcium Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
6	randomised trials	not serious	not serious	not serious [a,b]	serious [c]	none	**RR 1.08** (0.97 to 1.20)	⊕⊕⊕◯ MODERATE
Cardiovascular mortality								
2	randomised trials	not serious	serious [d]	not serious [a]	very serious [c]	none	**RR 1.24** (0.00 to 21640.00)	⊕◯◯◯ VERY LOW
MI								
4	randomised trials	not serious	very serious [d]	not serious [a]	very serious [c]	none	**RR 1.64** (0.75 to 3.62)	⊕◯◯◯ VERY LOW
Stroke								
3	randomised trials	not serious	not serious	not serious [a]	very serious [c]	none	**RR 1.29** (0.76 to 2.18)	⊕⊕◯◯ LOW
CHD								
2	randomised trials	not serious	not serious	not serious	very serious [c]	none	**RR 1.16** (0.44 to 3.05)	⊕⊕◯◯ LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

I. Calcium + Vitamin D Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
20	randomised trials	not serious	not serious	not serious [a,b]	serious [c]	none	**RR 0.95** (0.90 to 1.00)	⊕⊕⊕◯ MODERATE
Cardiovascular mortality								
1	randomised trials	not serious	not serious	not serious [a]	serious [c]	none	**RR 0.99** (0.95 to 1.03)	⊕⊕⊕◯ MODERATE
MI								
5	randomised trials	not serious	not serious	not serious [a]	serious [c]	none	**RR 1.14** (0.97 to 1.34)	⊕⊕⊕◯ MODERATE
Stroke								
7	randomised trials	not serious	not serious	not serious [a]	serious [c]	none	**RR 1.17** (1.05 to 1.30)	⊕⊕⊕◯ MODERATE
CHD								
2	randomised trials	not serious	not serious	not serious	very serious [c]	none	**RR 0.73** (0.00 to 3449.00)	⊕⊕◯◯ LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

m. Beta Carotene Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
6	randomised trials	not serious	not serious	not serious [a,b]	very serious [c]	none	**RR 1.03** (0.94 to 1.13)	⊕⊕◯◯ LOW
Cardiovascular mortality								
4	randomised trials	not serious	not serious	not serious [a]	very serious [c]	none	**RR 1.10** (0.93 to 1.30)	⊕⊕◯◯ LOW
MI								
3	randomised trials	not serious	not serious	not serious [a]	very serious [c]	none	**RR 0.99** (0.86 to 1.15)	⊕⊕◯◯ LOW
Stroke								
3	randomised trials	not serious	not serious	not serious [a]	**Stroke**	none	**RR 1.06** (0.83 to 1.35)	⊕⊕◯◯ LOW
CHD								
2	randomised trials	not serious	not serious	not serious	very serious [c]	none	**RR 1.02** (0.86 to 1.21)	⊕⊕◯◯ LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

n. Antioxidant Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
21	randomised trials	not serious	not serious	very serious [a,b]	very serious [c]	none	**RR 1.06** (0.99 to 1.12)	⊕◯◯◯ VERY LOW
Cardiovascular mortality								
7	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	**RR 1.02** (0.92 to 1.12)	⊕◯◯◯ VERY LOW
MI								
6	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	**RR 0.98** (0.87 to 1.11)	⊕◯◯◯ VERY LOW
Stroke								
7	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	**RR 1.00** (0.94 to 1.07)	⊕◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

o. Vitamin D Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
45	randomised trials	not serious	not serious	very serious [a,b]	not serious [c]	none [d]	**RR 0.99** (0.96 to 1.02)	⊕⊕◯◯ LOW
Cardiovascular mortality								
4	randomised trials	not serious	not serious [e]	very serious [a]	very serious [c]	none	**RR 1.00** (0.79 to 1.28)	⊕◯◯◯ VERY LOW
MI								
14	randomised trials	not serious	not serious [e]	very serious [a]	serious [c]	none	**RR 0.95** (0.88 to 1.03)	⊕◯◯◯ VERY LOW
Stroke								
13	randomised trials	not serious	not serious [e]	very serious [b]	serious [c]	none	**RR 1.06** (0.95 to 1.19)	⊕◯◯◯ VERY LOW
CHD								
5	randomised trials	not serious	not serious [e]	very serious [a]	very serious [c]	none	**RR 0.98** (0.87 to 1.10)	⊕◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

p. n-3 LC PUFA Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
41	randomised trials	not serious	not serious	serious [a,b]	serious [c]	publication bias strongly suspected [d]	**RR 0.98** (0.93 to 1.02)	⊕◯◯◯ VERY LOW
Cardiovascular mortality								
27	randomised trials	not serious	not serious [e]	serious [a]	serious [c]	none	**RR 0.93** (0.86 to 1.01)	⊕⊕◯◯ LOW
MI								
25	randomised trials	not serious	not serious [e]	serious [a]	serious [c]	none	**RR 0.92** (0.85 to 0.99)	⊕⊕◯◯ LOW
Stroke								
30	randomised trials	not serious	not serious	serious [a]	serious [c]	none	**RR 1.05** (0.97 to 1.13)	⊕⊕◯◯ LOW
CHD								
30	randomised trials	not serious	not serious	serious [a]	serious [c]	none	**RR 0.93** (0.89 to 0.98)	⊕⊕◯◯ LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

q. Modified Dietary Fat Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
8	randomised trials	not serious	very serious [a]	serious [b,c]	serious [d]	none [e]	**RR 1.02** (0.83 to 1.25)	⊕◯◯◯ VERY LOW
Cardiovascular mortality								
6	randomised trials	not serious	serious [a]	serious [b]	very serious [d]	none	**RR 0.92** (0.68 to 1.25)	⊕◯◯◯ VERY LOW
MI								
9	randomised trials	not serious	serious [a]	serious [b]	very serious [d]	none [e]	**RR 0.92** (0.66 to 1.28)	⊕◯◯◯ VERY LOW
Stroke								
4	randomised trials	not serious	not serious [a]	serious [c]	very serious [d]	none [e]	**RR 0.70** (0.24 to 2.07)	⊕◯◯◯ VERY LOW
CHD								
9	randomised trials	not serious	very serious [a]	serious [b]	very serious [d]	none	**RR 0.81** (0.58 to 1.14)	⊕◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

r. Reduced Salt Intake in Normotensive Patients Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
3	randomised trials	not serious	not serious [a]	not serious [b,c]	serious [d]	none [e]	**RR 0.90** (0.85 to 0.95)	⊕⊕⊕◯ MODERATE
CHD								
4	randomised trials	not serious	not serious [a]	not serious [b]	very serious [d]	none	**RR 0.97** (0.80 to 1.18)	⊕⊕◯◯ LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

s. Reduced Salt Intake in Hypertensive Patients Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
5	randomised trials	not serious	not serious [a]	not serious [b,c]	very serious [d]	none [e]	**RR 0.99** (0.92 to 1.07)	⊕⊕◯◯ LOW
Cardiovascular mortality								
3	randomised trials	not serious	not serious [a]	not serious [b]	serious [d]	none	**RR 0.67** (0.46 to 0.99)	⊕⊕⊕◯ MODERATE
CHD								
5	randomised trials	not serious	not serious [a]	not serious [b]	very serious [d]	none	**RR 0.95** (0.66 to 1.38)	⊕⊕◯◯ LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

t. Reduced Saturated Fat Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
10	randomised trials	not serious	not serious [a]	serious [b,c]	very serious [d]	publication bias strongly suspected [e]	**RR 0.97** (0.88 to 1.07)	⨁◯◯◯ VERY LOW
Cardiovascular mortality								
12	randomised trials	not serious	serious [a]	serious [b]	very serious [d]	none	**RR 0.95** (0.78 to 1.15)	⨁◯◯◯ VERY LOW
MI								
10	randomised trials	not serious	not serious [a]	serious [b]	serious [d]	none [e]	**RR 0.90** (0.80 to 1.01)	⨁⨁◯◯ LOW
Stroke								
7	randomised trials	not serious	not serious [a]	serious [c]	very serious [d]	none [e]	**RR 1.00** (0.89 to 1.12)	⨁◯◯◯ VERY LOW
CHD								
8	randomised trials	not serious	very serious [a]	serious [b]	serious [d]	none	**RR 0.87** (0.74 to 1.03)	⨁◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

u. Mediterranean Diet Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
5	randomised trials	not serious	very serious [a]	not serious [b,c]	very serious [d]	none [e]	**RR 0.81** (0.45 to 1.47)	⊕◯◯◯ VERY LOW
Cardiovascular mortality								
4	randomised trials	not serious	very serious [a]	not serious [b]	very serious [d]	none	**RR 0.68** (0.21 to 2.19)	⊕◯◯◯ VERY LOW
MI								
3	randomised trials	not serious	very serious [a]	not serious [b]	very serious [d]	none [e]	**RR 0.49** (0.12 to 1.95)	⊕◯◯◯ VERY LOW
Stroke								
3	randomised trials	not serious	not serious [a]	not serious [c]	very serious [d]	none [e]	**RR 0.65** (0.39 to 1.11)	⊕⊕◯◯ LOW
CHD								
3	randomised trials	not serious	very serious [a]	not serious [b]	very serious [d]	none	**RR 0.59** (0.18 to 1.98)	⊕◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

v. Reduced Dietary Fat Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
10	randomised trials	not serious	not serious [a]	serious [b,c]	serious [d]	none [e]	**RR 0.97** (0.92 to 1.02)	⊕⊕◯◯ LOW
Cardiovascular mortality								
7	randomised trials	not serious	not serious [a]	serious [b]	very serious [d]	none	**RR 0.96** (0.82 to 1.14)	⊕◯◯◯ VERY LOW
MI								
6	randomised trials	not serious	not serious [a]	serious [b]	very serious [d]	none [e]	**RR 0.97** (0.87 to 1.07)	⊕◯◯◯ VERY LOW
Stroke								
4	randomised trials	not serious	not serious [a]	serious [c]	very serious [d]	none [e]	**RR 1.01** (0.86 to 1.19)	⊕◯◯◯ VERY LOW
CHD								
8	randomised trials	not serious	not serious [a]	serious [b]	very serious [d]	none	**RR 0.97** (0.85 to 1.11)	⊕◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

w. n-6 PUFA Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
10	randomised trials	not serious	not serious [a]	serious [b,c]	very serious [d]	none [e]	**RR 1.00** (0.88 to 1.13)	⨁◯◯◯ VERY LOW
Cardiovascular mortality								
7	randomised trials	not serious	very serious [a]	serious [b]	very serious [d]	none	**RR 1.09** (0.68 to 1.75)	⨁◯◯◯ VERY LOW
MI								
7	randomised trials	not serious	serious [a]	serious [b]	serious [d]	none [e]	**RR 0.88** (0.75 to 1.03)	⨁◯◯◯ VERY LOW
Stroke								
4	randomised trials	not serious	very serious [a]	serious [c]	very serious [d]	none [e]	**RR 1.27** (0.28 to 5.87)	⨁◯◯◯ VERY LOW
CHD								
7	randomised trials	not serious	very serious [a]	serious [b]	very serious [d]	none	**RR 0.86** (0.50 to 1.46)	⨁◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

x. n-3 (ALA) PUFA Compared to Control for Mortality and Cardiovascular Outcomes

Certainty assessment							Effect	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative (95% CI)**	
All-cause mortality								
5	randomised trials	not serious	not serious [a]	serious [b,c]	very serious [d]	none [e]	**RR 1.01** (0.82 to 1.23)	⨁◯◯◯ VERY LOW
Cardiovascular mortality								
4	randomised trials	not serious	not serious [a]	serious [b]	very serious [d]	none	**RR 0.96** (0.80 to 1.15)	⨁◯◯◯ VERY LOW
MI								
3	randomised trials	not serious	serious [a]	serious [b]	very serious [d]	none [e]	**RR 1.00** (0.53 to 1.87)	⨁◯◯◯ VERY LOW
Stroke								
5	randomised trials	not serious	not serious [a]	serious [c]	very serious [d]	none [e]	**RR 1.15** (0.66 to 1.99)	⨁◯◯◯ VERY LOW
CHD								
4	randomised trials	not serious	not serious [a]	serious [b]	very serious [d]	none	**RR 1.00** (0.72 to 1.37)	⨁◯◯◯ VERY LOW

a. Indirectness was considered serious if cumulative evidence was derived from trials assessing interventions in participants with varying baseline cardiovascular risk, i.e. primary or secondary prevention trials, b. Indirectness was considered very serious if cumulative evidence was derived from trials assessing interventions in participants with wide variety of indications i.e. non cardiovascular diseases and cardiovascular diseases, c. Serious imprecision was considered if the 95% confidence intervals overlaps with the minimally important difference for clinical benefit (RR<0.95) or harm (RR>1.05). Very serious imprecision was considered if the 95% confidence intervals include both clinically important benefit (RR<0.95) and harm (RR>1.05).

Supplement Table 6. Characteristics of the Included Interventions Extracted From Selected Systematic Reviews

Intervention	Trials	No. Of Participants	Age (years)	Women (%)	Hypertension (%)	Diabetes (%)	CAD (%)	Follow–up (months)
Vitamin E	35	137,179	18-90	NR	NR	NR	NR	6-125
Vitamin C	4	16,004	18-69	NR	NR	NR	NR	15-125
Vitamin B Complex	16	45,424	18-89	NR	NR	NR	NR	6-88
Vitamin B6	2	3,429	NR	NR	NR	NR	NR	38.4-39.6
Vitamin B3/ Niacin	8	34,543	18-80	NR	NR	NR	NR	6-74
Vitamin A	1	2,297	45-74	NR	NR	NR	NR	36-48
Selenium	5	19,454	26-75	NR	NR	NR	NR	6-91
Multivitamins	10	22,869	40-85	NR	NR	NR	NR	12-134
Iron	2	762	NR	NR	NR	NR	NR	NR
Folic acid	12	28,483	18-79	NR	NR	NR	NR	12-120
Calcium	6	9,765	60-97	NR	NR	NR	NR	24-96
Calcium + Vitamin D	20	42,072	33-103	NR	NR	NR	NR	6-86
β-carotene	8	63,946	20-84	NR	NR	NR	NR	25-144
Antioxidants	24	73,262	18-80	NR	NR	NR	NR	6-125
Vitamin D	50	69,503	18-104	NR	NR	NR	NR	6-66
n 3 LC PUFA	51	135,663	61.4	63.2	47.0	35-100	17.7	28.6
Modified dietary fat	12	12,313	49.4	23	NR	0-100	0-100	20.3
*Reduced salt (hypertensives/ normotensives)	10	35,945	55.8	43.5	55.5	NR	NR	38.9
Reduced saturated fat	15	56,195	48.8	65.08	NR	0-100	0-100	26.1
Mediterranean diet	5	10,671	54	33.3	66.6	39.4	10.8	25.4
Reduced dietary fat	12	60,642	48.9	94.6	NR	0-100	0-100	25
n-6 PUFA	13	5,786	51.9	32.32	10.3	4.3	54.2	24.2
n- 3 (ALA) PUFA	5	19,483	62.6	46	3.0	NR	12.5	20.6

Values are given as ranges, median or mean which ever was available. NR = Not Reported, * represents both (hypertensives and normotensive groups), LC (long chain), n-3 (omega 3), n-6 (omega 6), PUFA (Polyunsaturated fatty acid)

Supplement Table 7. Eggers' Regression Test and Degree of Heterogeneity

Outcome	Intervention	Egger's P-value	I^2
All-cause mortality	Vitamin E	0.31	0%
	Vitamin C	ND	0%
	Vitamin B-Complex	0.46	0%
	Vitamin B6	ND	0%
	Vitamin B3/Niacin	ND	0%
	Vitamin A	ND	NA
	Selenium	ND	0%
	Multivitamins	0.51	0%
	Iron	ND	0%
	Folic acid	0.31	17%
	Calcium	ND	0%
	Calcium +Vitamin D	0.33	0%
	Beta carotene	ND	10%
	Antioxidant	0.21	17%
	Vitamin D	0.72	0%
	n-3 (LC) PUFA	0.09	8.5%
	Modified fat intake	ND	34%
	Reduced salt (normotensive)	ND	0%
	Reduced salt (hypertensive)	ND	0%
	Reduced saturared fat intake	0.02	3%
	Mediterranean diet	ND	68%
	Reduced dietary fat intake	ND	0%
	n-6 PUFA	0.76	0%
	n-3 (ALA) PUFA	ND	0%
Cardiovascular mortality	Vitamin E	0.14	0%
	Vitamin C	ND	0%
	Vitamin B-Complex	ND	52%
	Vitamin B3/Niacin	ND	0%
	Selenium	ND	48%
	Multivitamins	ND	0%

	Iron	ND	0%
	Folic acid	ND	0%
	Calcium	ND	53%
	Calcium +Vitamin D	ND	NA
	Beta carotene	ND	0%
	Antioxidant	ND	0%
	Vitamin D	ND	0%
	N-3 (LC) PUFA	0.14	23%
	Modified dietary fat	ND	45%
	Reduced salt (hypertensive)	ND	0%
	Reduced saturared fat	ND	30%
	Mediterranean diet	ND	77%
	Reduced dietary fat	ND	0%
	n-6 PUFA	ND	61%
	n-3 (ALA) PUFA	ND	0%
MI	Vitamin E	0.01	64%
	Vitamin C	ND	6%
	Vitamin B-Complex	0.92	0%
	Vitamin B6	ND	0%
	Vitamin B3/Niacin	ND	38%
	Selenium	ND	0%
	Multivitamins	ND	0%
	Folic acid	ND	12%
	Calcium	ND	69%
	Calcium +Vitamin D	ND	0%
	Beta carotene	ND	0%
	Antioxidant	ND	0%
	Vitamin D	0.75	0%
	n-3 (LC) PUFA	0.11	1%
	Modified dietary fat	ND	45%
	Reduced saturared fat	ND	10%
	Mediterranean diet	ND	64%
	Reduced dietary fat	ND	0%

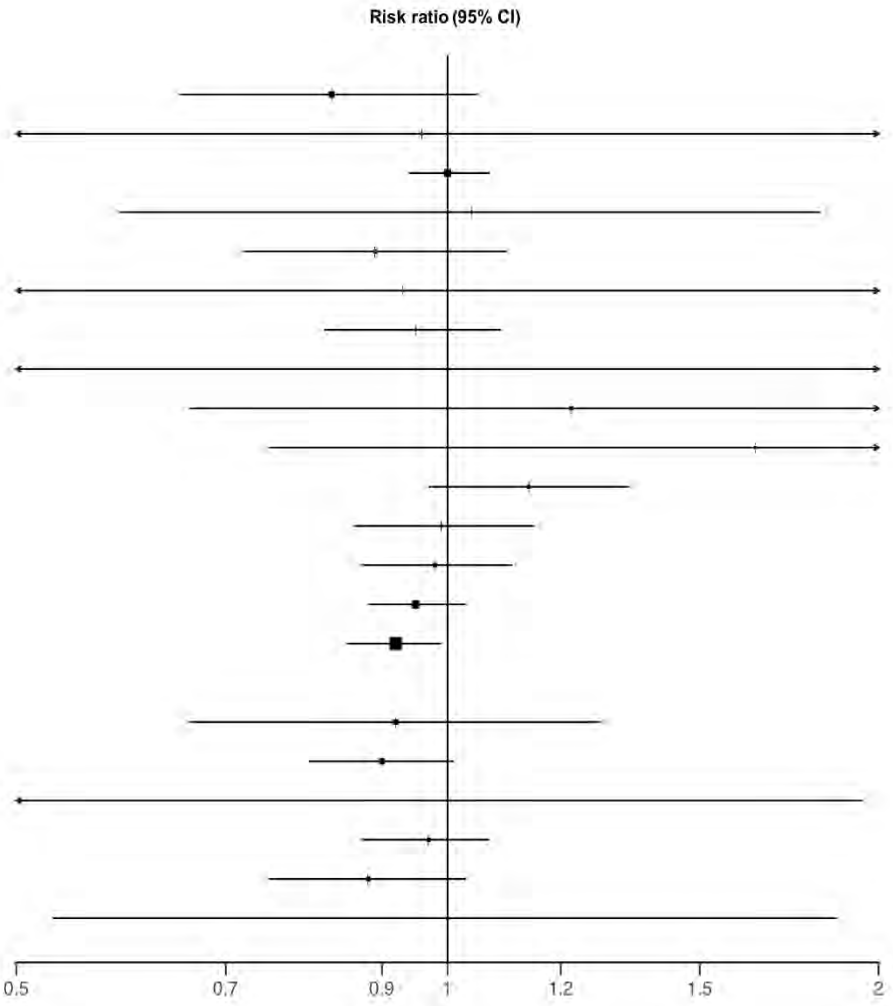
	n-6 PUFA	ND	0%
	n-3 (ALA) PUFA	ND	26%
Stroke	Vitamin E	0.08	15%
	Vitamin C	ND	0%
	Vitamin B-Complex	0.48	16%
	Vitamin B6	ND	0%
	Vitamin B3/Niacin	ND	60%
	Selenium	ND	0%
	Multivitamins	ND	59%
	Folic acid	ND	0%
	Calcium	ND	0%
	Calcium +Vitamin D	ND	0%
	Beta carotene	ND	36%
	Antioxidant	ND	0%
	Vitamin D	0.24	0%
	n-3 (LC) PUFA	0.15	0%
	Modified dietary fat	ND	8%
	Reduced saturared fat	ND	0%
	Mediterranean diet	ND	0%
	Reduced dietary fat	ND	0%
	n-6 PUFA	ND	56%
	n-3 (ALA) PUFA	ND	0%
CHD	Vitamin E	ND	0%
	Vitamin C	ND	NA
	Vitamin B-Complex	ND	12%
	Vitamin B3/Niacin	ND	0%
	Selenium	ND	NA
	Folic acid	ND	0%
	Calcium	ND	53%
	Calcium +Vitamin D	ND	49%
	Beta carotene	ND	0%
	Vitamin D	ND	0%
	n-3 (LC) PUFA	0.49	0.6%

	Modified dietary fat	ND	61%
	Reduced salt (normotensive)	ND	0%
	Reduced salt (hypertensive)	ND	0%
	Reduced saturared fat	ND	66%
	Mediterranean diet	ND	62%
	Reduced dietary fat	ND	17%
	n-6 PUFA	ND	71%
	n-3 (ALA) PUFA	ND	2%

CHD (Coronary Heart Disease); MI (Myocardial infarction); ND (Not Determined); NA (Not Applicable)

Supplement Figure 1: Forest plot showing effects of nutritional supplements and dietary interventions on myocardial infarction

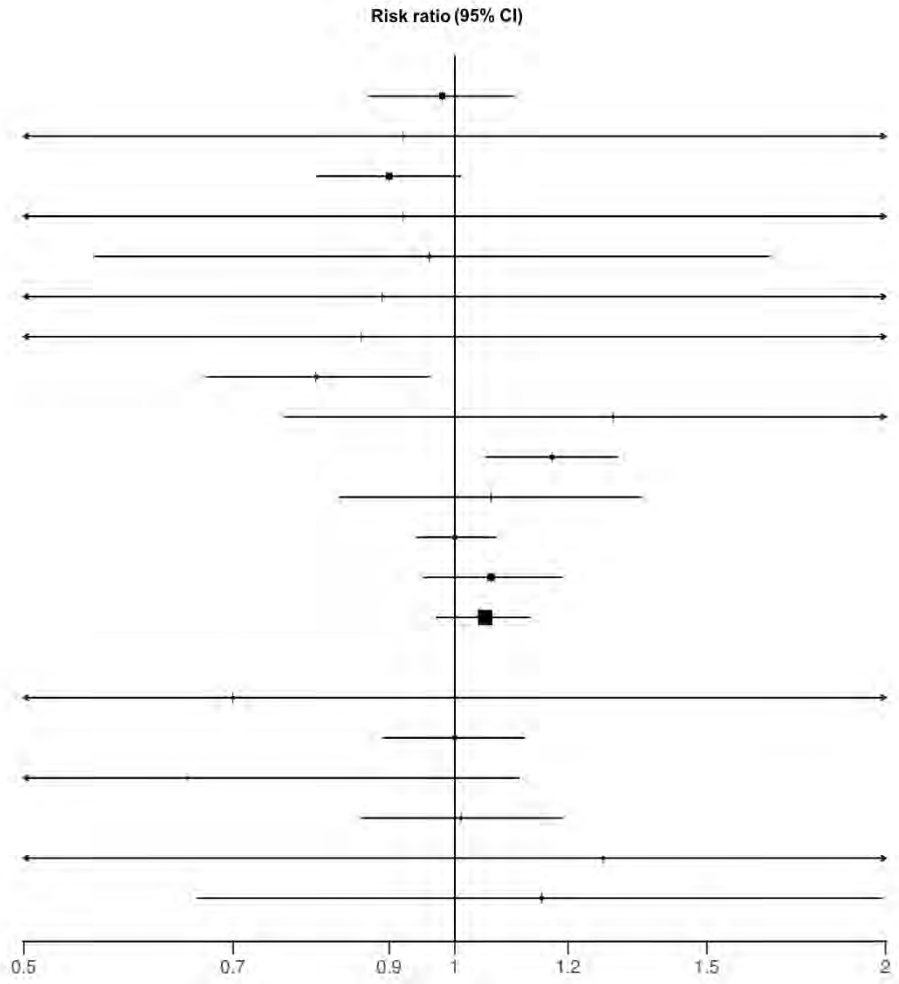
Intervention	Author, year	No. of studies	No. of events	No. of participants	Risk ratio (95% CI)
Nutritional supplements					
Vitamin E	Jenkins D, 2018 (1)	10	3,119	87,049	0.83 (0.65, 1.05)
Vitamin C	Jenkins D, 2018 (1)	2	545	15,497	0.96 (0.32, 2.89)
Vitamin B complex	Jenkins D, 2018 (1)	13	2,875	44,285	1.00 (0.94, 1.07)
Vitamin B6	Jenkins D, 2018 (1)	2	427	3,429	1.04 (0.59, 1.82)
Vitamin B3 / niacin	Jenkins D & Riaz, 2018 (1-2)	6	1,541	34,292	0.89 (0.72, 1.10)
Selenium	Jenkins D, 2018 (1)	2	87	1,085	0.93 (0.25, 3.45)
Multivitamins	Jenkins D, 2018 (1)	3	772	16,414	0.95 (0.82, 1.09)
Iron	Jenkins D, 2018 (1)	1	5	459	0.34 (0.06, 2.01)
Folic Acid	Jenkins D, 2018 (1)	6	106	24,210	1.22 (0.66, 2.24)
Calcium	Jenkins D, 2018 (1)	4	231	5,387	1.64 (0.75, 3.62)
Ca + Vitamin D	Jenkins D, 2018 (1)	5	453	19,097	1.14 (0.97, 1.34)
Beta carotene	Jenkins D, 2018 (1)	3	1,841	43,912	0.99 (0.86, 1.15)
Antioxidants	Jenkins D, 2018 (1)	6	1,815	42,134	0.98 (0.87, 1.11)
Vitamin D	Khan S, 2019*	14	1,047	42,068	0.95 (0.88, 1.03)
n-3 LC PUFA	Khan S, 2019*	25	2,931	113,510	0.92 (0.85, 0.99)
Dietary interventions					
Modified dietary fat	Hooper L, 2012 (8)	9	579	11,831	0.92 (0.66, 1.28)
Reduced saturated fat	Hooper L, 2016 (9)	10	1,714	53,167	0.90 (0.80, 1.01)
Mediterranean diet	Liyanage T, 2016 (5)	3	120	7,009	0.49 (0.12, 1.95)
Reduced dietary fat	Hooper L, 2018 (6)	6	1,203	50,522	0.97 (0.87, 1.07)
n-6 PUFA	Hooper L, 2018 (4)	7	609	4,606	0.88 (0.75, 1.03)
n-3 ALA PUFA	Abdelhamid A, 2018 (3)	3	333	18,353	1.00 (0.53, 1.87)



ALA (Alpha Linolenic Acid), Ca (Calcium), LC (Long Chain), n-3 (omega 3), n-6 (omega 6), PUFA (Polyunsaturated Fatty Acid). * *Updated meta-analysis after inclusion of new clinical trials*

Supplement Figure 2: Forest plot showing effects of nutritional supplements and dietary interventions on stroke

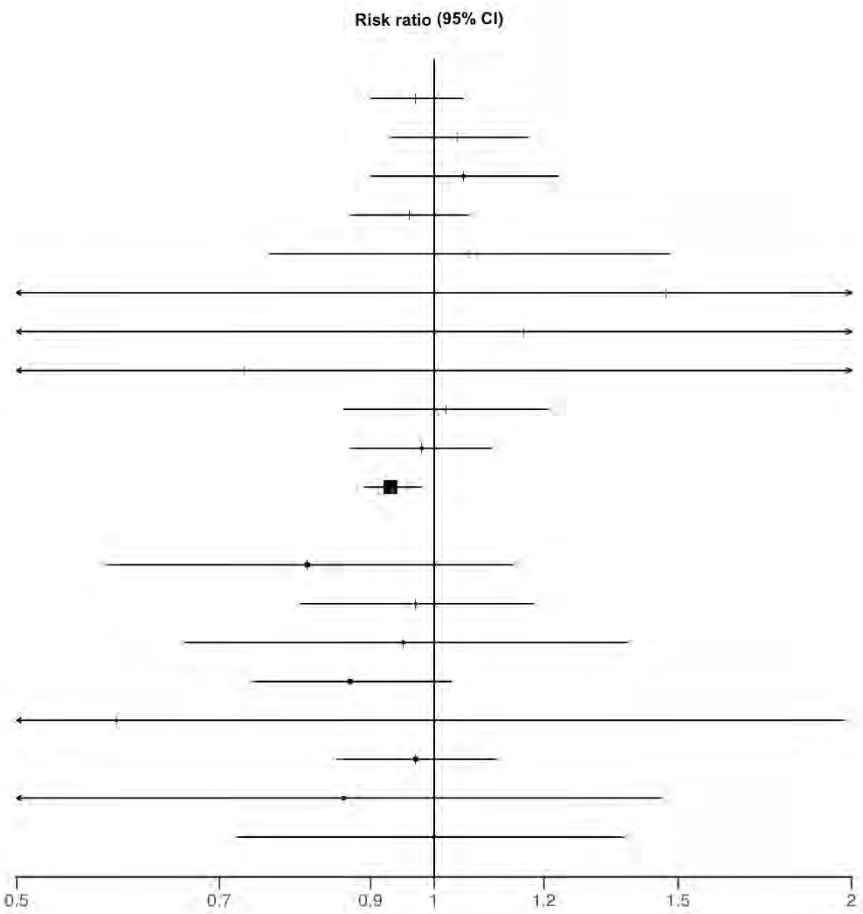
Intervention	Author, year	No. of studies	No. of events	No. of participants	Risk ratio (95% CI)
Nutritional supplements					
Vitamin E	Jenkins D, 2018 (1)	11	1,956	100,575	0.98 (0.87, 1.10)
Vitamin C	Jenkins D, 2018 (1)	2	525	15,497	0.92 (0.35, 2.40)
Vitamin B complex	Jenkins D, 2018 (1)	12	2,067	43,339	0.90 (0.80, 1.01)
Vitamin B6	Jenkins D, 2018 (1)	2	88	3,429	0.92 (0.18, 4.67)
Vitamin B3 / niacin	Jenkins D & Riaz, 2018 (1-2)	5	1,453	34,104	0.96 (0.56, 1.66)
Selenium	Jenkins D, 2018 (1)	2	249	18,770	0.89 (0.19, 4.27)
Multivitamins	Jenkins D, 2018 (1)	2	666	16,349	0.86 (0.01, >10.0)
Folic Acid	Jenkins D, 2018 (1)	7	694	24,525	0.80 (0.67, 0.96)
Calcium	Jenkins D, 2018 (1)	3	178	3,861	1.29 (0.76, 2.18)
Ca + Vitamin D	Jenkins D, 2018 (1)	7	484	19,227	1.17 (1.05, 1.30)
Beta carotene	Jenkins D, 2018 (1)	3	2,104	58,761	1.06 (0.83, 1.35)
Antioxidants	Jenkins D, 2018 (1)	7	1,986	60,589	1.00 (0.94, 1.07)
Vitamin D	Khan S, 2019*	13	822	42,060	1.06 (0.95, 1.19)
n-3 LC PUFA	Khan S, 2019*	30	2,543	130,709	1.05 (0.97, 1.13)
Dietary interventions					
Modified dietary fat	Hooper L, 2012 (8)	4	51	10,315	0.70 (0.24, 2.07)
Reduced saturated fat	Hooper L, 2016 (9)	7	1,125	50,952	1.00 (0.89, 1.12)
Mediterranean diet	Liyanage T, 2016 (5)	3	167	9,052	0.65 (0.39, 1.11)
Reduced dietary fat	Hooper L, 2018 (8)	4	1,084	49,246	1.01 (0.86, 1.19)
n-6 PUFA	Hooper L, 2018 (4)	4	54	3,730	1.27 (0.28, 5.87)
n-3 ALA PUFA	Abdelhamid A, 2018 (3)	5	51	19,327	1.15 (0.66, 1.99)



ALA (Alpha Linolenic Acid), Ca (Calcium), LC (Long Chain), n-3 (omega 3), n-6 (omega 6), PUFA (Polyunsaturated Fatty Acid). * *Updated meta-analysis after inclusion of new clinical trials*

Supplement Figure 3: Forest plot showing effects of nutritional supplements and dietary interventions on coronary heart disease

Intervention	Author, year	No. of studies	No. of events	No. of participants	Risk ratio (95% CI)
Nutritional supplements					
Vitamin E	Jenkins D, 2018 (1)	2	2,052	21,840	0.97 (0.90, 1.05)
Vitamin C	Jenkins D, 2018 (1)	1	1,045	8,171	1.04 (0.93, 1.17)
Vitamin B complex	Jenkins D, 2018 (1)	5	3,197	20,886	1.05 (0.90, 1.23)
Vitamin B3 / niacin	Jenkins D, 2018 (1)	2	1,363	26,615	0.96 (0.87, 1.06)
Selenium	Jenkins D, 2018 (1)	1	122	1,004	1.06 (0.76, 1.48)
Folic Acid	Jenkins D, 2018 (1)	2	77	2,197	1.47 (0.10, >10.0)
Calcium	Jenkins D, 2018 (1)	2	166	3,171	1.16 (0.44, 3.05)
Ca + Vitamin D	Jenkins D, 2018 (1)	2	445	15,390	0.73 (0.00, >10.0)
Beta carotene	Jenkins D, 2018 (1)	2	2,081	21,841	1.02 (0.86, 1.21)
Vitamin D	Khan S, 2019*	5	849	31,413	0.98 (0.87, 1.10)
n-3 LC PUFA	Khan S, 2019*	30	7,298	113,248	0.93 (0.89, 0.98)
Dietary interventions					
Modified dietary fat	Hooper L, 2012 (8)	9	855	11,660	0.81 (0.58, 1.14)
Reduced salt (normotensive)	Alder A, 2014; Mente A, 2016 (6-7)	4	NA	2,415	0.97 (0.80, 1.18)
Reduced salt (hypertensive)	Alder A, 2014; Mente A, 2016 (6-7)	5	NA	1,416	0.95 (0.66, 1.38)
Reduced saturated fat	Hooper L, 2016 (9)	8	4,377	53,199	0.87 (0.74, 1.03)
Mediterranean diet	Liyanage T, 2016 (5)	3	221	9,052	0.59 (0.18, 1.98)
Reduced dietary fat	Hooper L, 2018 (8)	8	3,632	50,655	0.97 (0.85, 1.11)
n-6 PUFA	Hooper L, 2018 (4)	7	1,059	3,997	0.86 (0.50, 1.46)
n-3 ALA PUFA	Abdelhamid A, 2018 (3)	4	397	19,061	1.00 (0.72, 1.37)

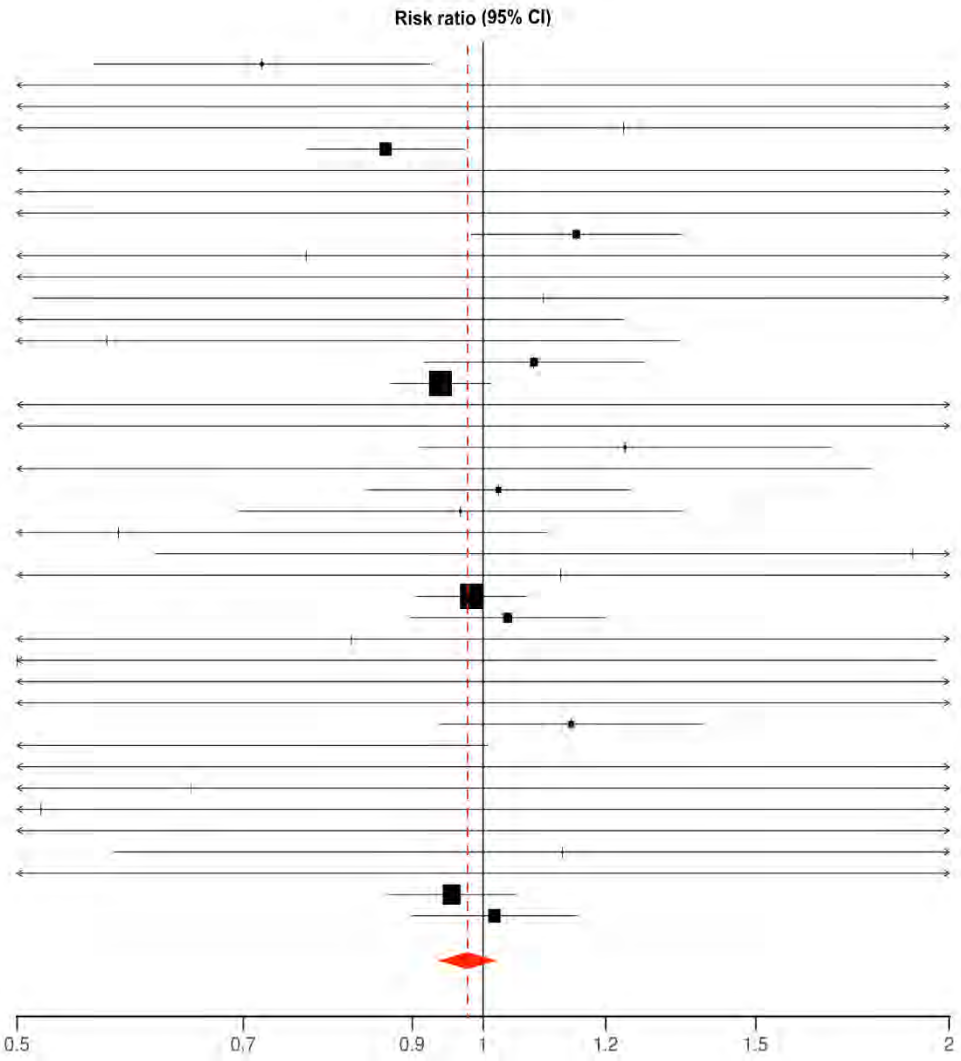


ALA (Alpha Linolenic Acid), Ca (Calcium), LC (Long Chain), n-3 (omega 3), n-6 (omega 6), NA (Not Available); PUFA (Polyunsaturated Fatty Acid).

**Updated meta-analysis after inclusion of new clinical trials*

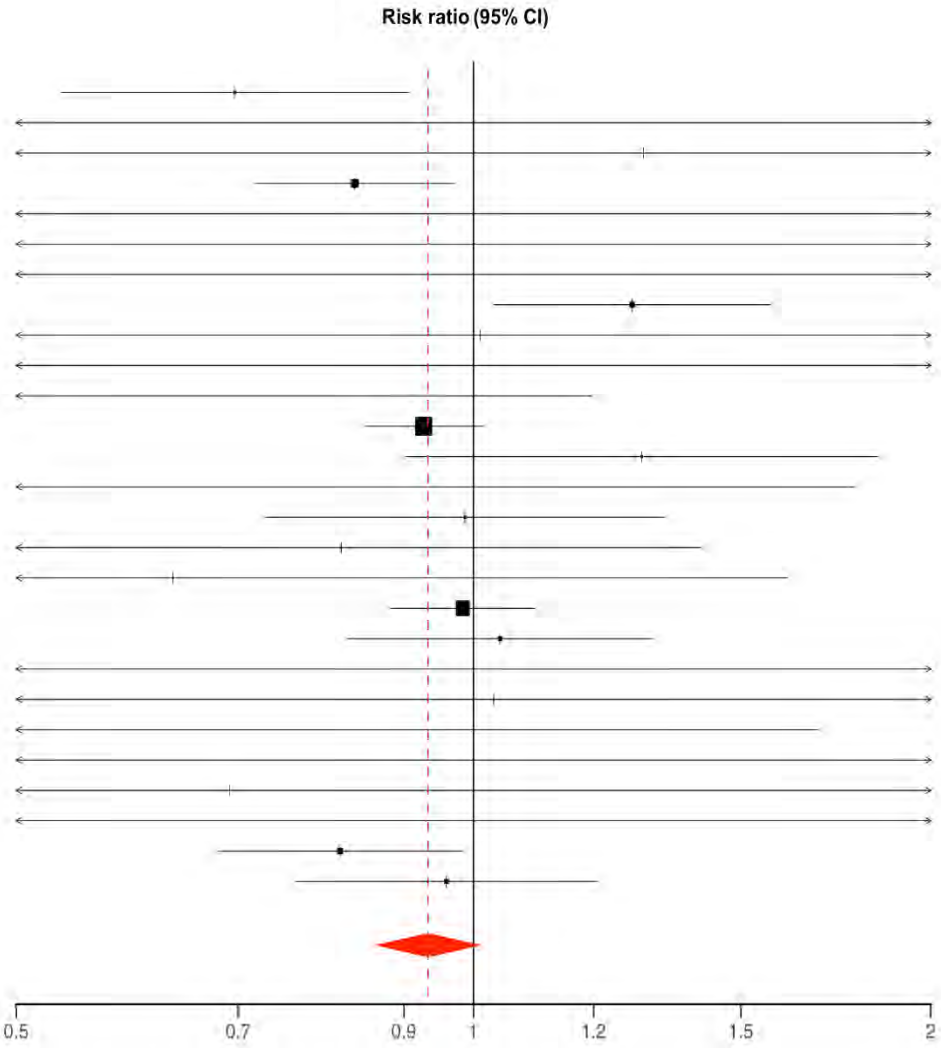
Supplement Figure 4: Forest plot showing effects of n-3 long chain polyunsaturated fatty acids (LC PUFA) on all-cause mortality

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk ratio (95% CI)
DART, 1989	94	1,015	131	1,018	0.72 (0.56, 0.92)
Bates, 1989	1	155	0	157	3.04 (0.12, >10.0)
HARP, 1995	0	41	1	39	0.32 (0.01, 7.56)
SHOT, 1996	8	317	6	293	1.23 (0.43, 3.51)
GISSI-P, 1999	472	5,666	545	5,658	0.86 (0.77, 0.97)
SCIMO, 1999	1	112	2	111	0.50 (0.05, 5.39)
OFAMI, 2001	11	150	11	150	1.00 (0.45, 2.24)
Brox, 2001	0	80	1	40	0.17 (0.01, 4.03)
DART-2, 2003	283	1,571	242	1,543	1.15 (0.98, 1.34)
DISAF, 2003	6	201	8	206	0.77 (0.27, 2.18)
Berson, 2004	0	105	1	103	0.33 (0.01, 7.94)
FAAT, 2005	13	200	12	202	1.09 (0.51, 2.34)
Raitt, 2005	4	100	10	100	0.40 (0.13, 1.23)
SOFA, 2006	8	273	14	273	0.57 (0.24, 1.34)
JELIS, 2007	286	9,326	265	9,319	1.08 (0.91, 1.27)
GISSI-HF, 2008	955	3,494	1,014	3,481	0.94 (0.87, 1.01)
EPIC-1, 2008	1	183	0	180	2.95 (0.12, >10.0)
EPIC-2, 2008	0	189	1	190	0.34 (0.01, 8.17)
OMEGA, 2009	88	1,919	70	1,885	1.23 (0.91, 1.68)
Nutristroke, 2009	0	38	4	34	0.10 (0.01, 1.78)
AlphaOmega EPA+DHA, 2010	186	2,404	184	2,433	1.02 (0.84, 1.24)
SU.FOL.OM3, 2010	66	1,253	68	1,248	0.97 (0.70, 1.34)
DO IT, 2010	14	282	24	281	0.58 (0.31, 1.10)
ADCS, 2010	11	238	4	164	1.89 (0.61, 5.85)
OPAL, 2010	9	434	8	433	1.12 (0.44, 2.88)
ORIGIN, 2012	951	6,281	964	6,255	0.98 (0.90, 1.07)
Risk % Prevention, 2013	348	6,239	337	6,266	1.04 (0.90, 1.20)
FORWARD, 2013	4	289	5	297	0.82 (0.22, 3.03)
NAT2, 2013	3	150	6	150	0.50 (0.13, 1.96)
Kumar, 2013	1	39	1	39	1.00 (0.06, >10.0)
AFFORD, 2013	0	153	1	163	0.36 (0.01, 8.65)
AREDS2, 2014	200	2,147	168	2,056	1.14 (0.94, 1.39)
Doi, 2014	2	119	9	119	0.22 (0.05, 1.01)
Shinto, 2014	1	13	1	13	1.00 (0.07, >10.0)
DIPP, 2015	2	104	3	101	0.65 (0.11, 3.79)
Derosa, 2016	1	138	2	143	0.52 (0.05, 5.65)
FOSTAR, 2016	0	101	1	101	0.33 (0.01, 8.09)
MAPT, 2017	18	840	16	840	1.12 (0.58, 2.19)
Zhang, 2017	0	120	1	120	0.33 (0.01, 8.10)
ASCEND, 2018	752	7,740	788	7,740	0.95 (0.87, 1.05)
VITAL, 2018	493	12,933	485	12,938	1.02 (0.90, 1.15)
Overall	**5,293**	**67,152**	**5,414**	**66,882**	**0.98 (0.93, 1.02)**



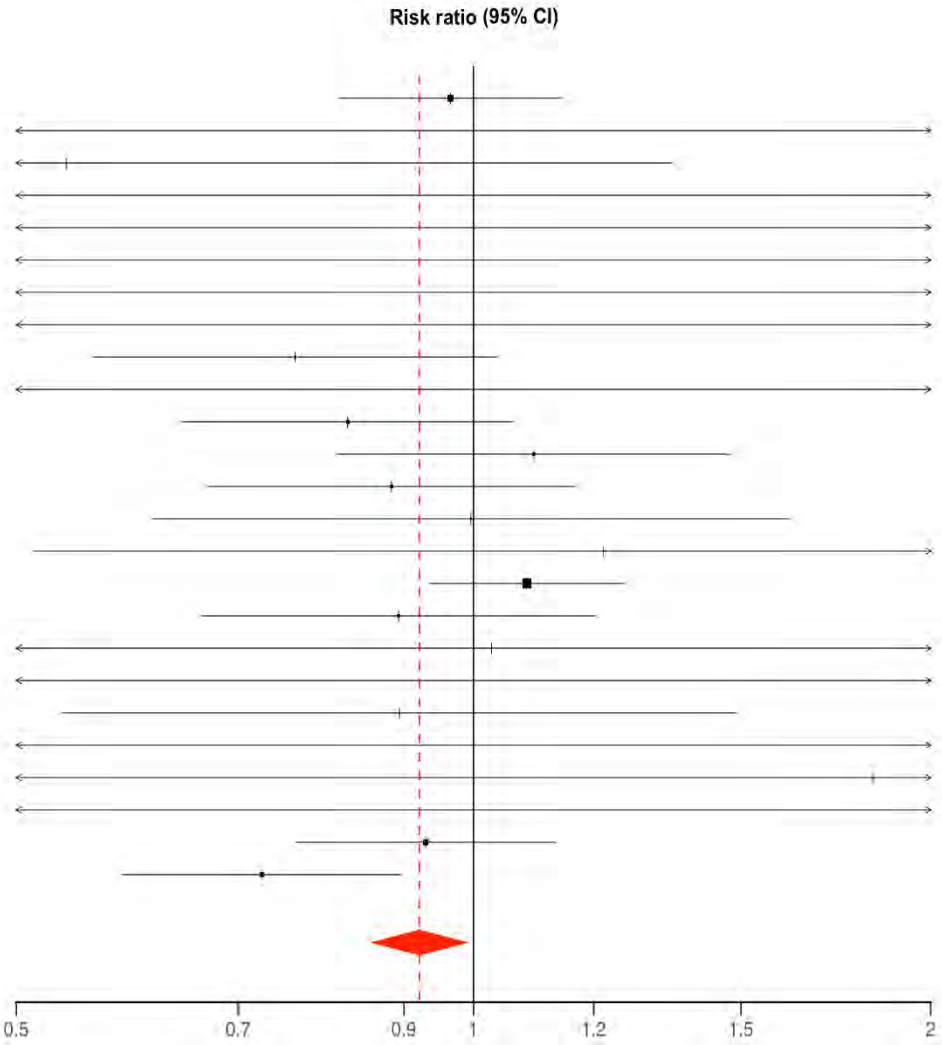
Supplement Figure 5: Forest plot showing effects of n-3 long chain polyunsaturated fatty acids (LC PUFA) on cardiovascular mortality

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk ratio (95% CI)
DART, 1989	84	1,015	121	1,018	0.70 (0.53, 0.91)
HARP, 1995	0	41	1	39	0.32 (0.01, 7.56)
SHOT, 1996	7	317	5	293	1.29 (0.42, 4.03)
GISSI-P, 1999	291	5,665	348	5,658	0.84 (0.72, 0.97)
SCIMO, 1999	0	112	1	111	0.33 (0.01, 8.02)
OFAMI, 2001	8	150	8	150	1.00 (0.39, 2.59)
Brox, 2001	0	80	1	40	0.17 (0.01, 4.03)
DART-2, 2003	180	1,571	139	1,543	1.27 (1.03, 1.57)
FAAT, 2005	9	200	9	202	1.01 (0.41, 2.49)
Raitt, 2005	2	100	5	100	0.40 (0.08, 2.01)
SOFA, 2006	6	273	13	273	0.46 (0.18, 1.20)
GISSI-HF, 2008	712	3,494	765	3,481	0.93 (0.85, 1.02)
OMEGA, 2009	67	1,919	51	1,885	1.29 (0.90, 1.85)
Nutristroke, 2009	0	38	4	34	0.10 (0.01, 1.78)
AlphaOmega EPA+DHA, 2010	80	2,404	82	2,433	0.99 (0.73, 1.34)
SU.FOL.OM3, 2010	23	1,253	28	1,248	0.82 (0.47, 1.41)
DO IT, 2010	7	282	11	281	0.63 (0.25, 1.61)
ORIGIN, 2012	574	6,281	581	6,255	0.98 (0.88, 1.10)
Risk % Prevention, 2013	142	6,239	137	6,266	1.04 (0.83, 1.31)
Kumar, 2013	1	39	1	39	1.00 (0.06, >10.0)
AREDS2, 2014	14	2,147	13	2,056	1.03 (0.49, 2.19)
Doi, 2014	1	119	5	119	0.20 (0.02, 1.69)
Shinto, 2014	1	13	0	13	3.00 (0.13, >10.0)
Derosa, 2016	2	138	3	143	0.69 (0.12, 4.07)
FOSTAR, 2016	0	101	1	101	0.33 (0.01, 8.09)
ASCEND, 2018	196	7,740	240	7,740	0.82 (0.68, 0.98)
VITAL, 2018	142	12,933	148	12,938	0.96 (0.76, 1.21)
Overall	**2,549**	**54,664**	**2,721**	**54,459**	**0.93 (0.86, 1.01)**



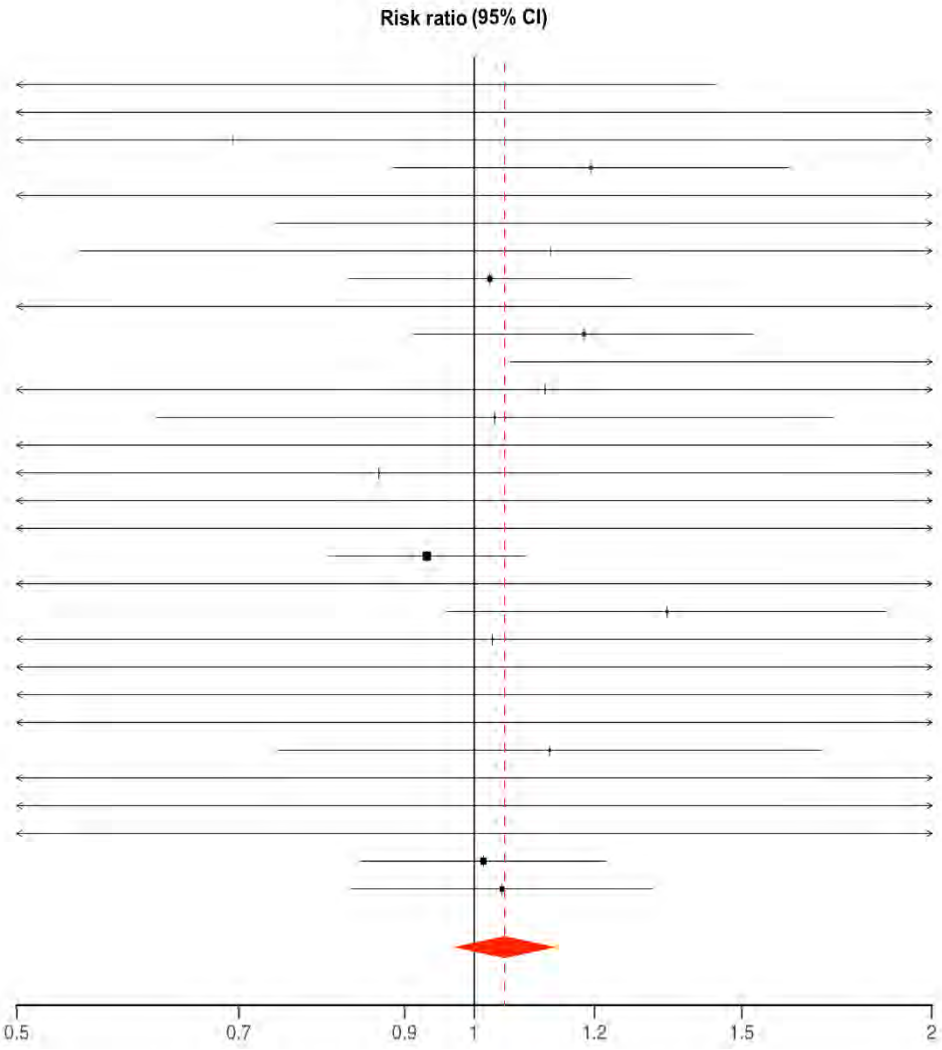
Supplement Figure 6: Forest plot showing effects n-3 long chain polyunsaturated fatty acids (LC PUFA) on myocardial infarction

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk ratio (95% CI)
DART, 1989	207	1,015	215	1,018	0.97 (0.81, 1.14)
HARP, 1995	1	41	3	39	0.32 (0.03, 2.92)
SHOT, 1996	7	317	12	293	0.54 (0.22, 1.35)
SCIMO, 1999	1	112	4	111	0.25 (0.03, 2.18)
Brox, 2001	0	80	1	40	0.17 (0.01, 4.03)
Raitt, 2005	1	100	3	100	0.33 (0.04, 3.15)
Baldassarre, 2006	1	32	0	32	3.00 (0.13, >10.0)
SOFA, 2006	1	273	3	273	0.33 (0.03, 3.18)
JELIS, 2007	71	9,326	93	9,319	0.76 (0.56, 1.04)
THIS DIET, 2008	1	51	3	50	0.33 (0.04, 3.04)
GISSI-HF, 2008	107	3,494	129	3,481	0.83 (0.64, 1.06)
OMEGA, 2009	87	1,919	78	1,885	1.10 (0.81, 1.48)
AlphaOmega EPA+DHA, 2010	89	2,404	102	2,433	0.88 (0.67, 1.17)
SU.FOL.OM3, 2010	32	1,253	32	1,248	1.00 (0.61, 1.62)
DO IT, 2010	11	282	9	281	1.22 (0.51, 2.89)
ORIGIN, 2012	344	6,281	316	6,255	1.08 (0.93, 1.26)
Risk % Prevention, 2013	80	6,239	90	6,266	0.89 (0.66, 1.20)
FORWARD, 2013	1	289	1	297	1.03 (0.06, >10.0)
EPOCH, 2014	1	195	0	196	3.02 (0.12, >10.0)
AREDS2, 2014	28	2,147	30	2,056	0.89 (0.54, 1.49)
Doi, 2014	1	119	0	119	3.00 (0.12, >10.0)
Proudman, 2015	1	87	0	53	1.83 (0.08, >10.0)
Derosa, 2016	0	128	3	130	0.15 (0.01, 2.78)
ASCEND, 2018	186	7,740	200	7,740	0.93 (0.76, 1.13)
VITAL, 2018	145	12,933	200	12,938	0.73 (0.59, 0.90)
Overall	**1,404**	**56,857**	**1,527**	**56,653**	**0.92 (0.85, 0.99)**



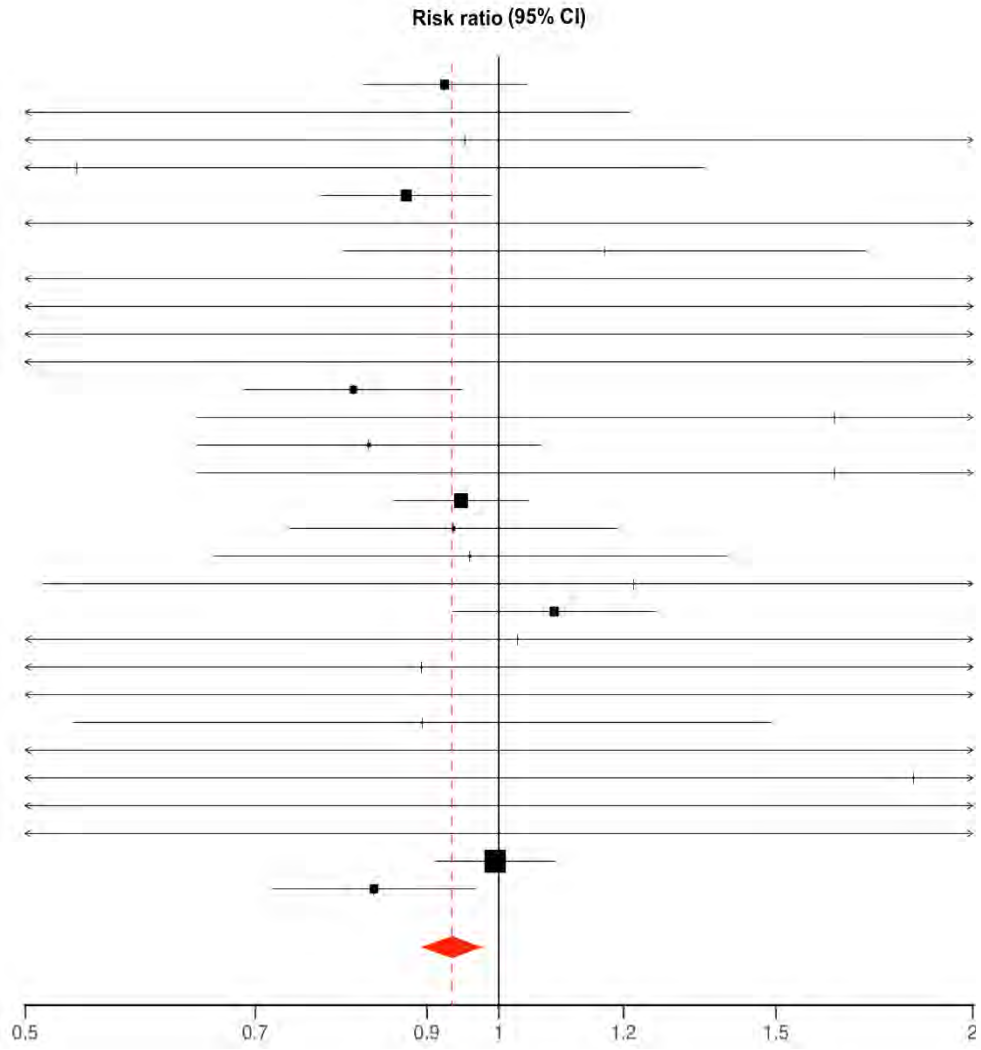
Supplement Figure 7: Forest plot showing effects of n-3 long chain polyunsaturated fatty acids (LC PUFA) on stroke

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk ratio (95% CI)
DART, 1989	4	1,015	9	1,018	0.45 (0.14, 1.44)
HARP, 1995	1	41	0	39	2.86 (0.12, >10.0)
SHOT, 1996	3	317	4	293	0.69 (0.16, 3.07)
GISSI-P, 1999	92	5,665	77	5,658	1.19 (0.88, 1.61)
SCIMO, 1999	1	112	0	111	2.97 (0.12, >10.0)
OFAMI, 2001	6	150	0	150	13.00 (0.74, >10.0)
DART-2, 2003	16	1,571	14	1,543	1.12 (0.55, 2.29)
JELIS, 2007	166	9,326	162	9,319	1.02 (0.83, 1.27)
THIS DIET, 2008	3	51	1	50	2.94 (0.32, >10.0)
GISSI-HF, 2008	122	3,494	103	3,481	1.18 (0.91, 1.53)
OMEGA, 2009	27	1,919	13	1,885	2.04 (1.06, 3.94)
AlphaOmega EPA+DHA, 2010	11	2,404	10	2,433	1.11 (0.47, 2.62)
SU.FOL.OM3, 2010	29	1,253	28	1,248	1.03 (0.62, 1.72)
DO IT, 2010	0	282	2	281	0.20 (0.01, 4.13)
OPAL, 2010	7	376	8	372	0.87 (0.32, 2.36)
Ozaydin, 2011	1	23	0	24	3.13 (0.13, >10.0)
Nodari HF, 2011	0	67	1	66	0.33 (0.01, 7.92)
ORIGIN, 2012	314	6,281	336	6,255	0.93 (0.80, 1.08)
ORL, 2013	2	171	0	165	4.83 (0.23, >10.0)
Risk % Prevention, 2013	80	6,239	60	6,266	1.34 (0.96, 1.87)
FORWARD, 2013	3	289	3	297	1.03 (0.21, 5.05)
NAT2, 2013	0	150	1	150	0.33 (0.01, 8.12)
AFFORD, 2013	1	153	0	163	3.20 (0.13, >10.0)
EPOCH, 2014	2	195	0	196	5.03 (0.24, >10.0)
AREDS2, 2014	48	2,147	41	2,056	1.12 (0.74, 1.69)
Doi, 2014	0	119	4	119	0.11 (0.01, 2.04)
Derosa, 2016	0	128	1	130	0.34 (0.01, 8.23)
MAPT, 2017	1	820	4	832	0.25 (0.03, 2.26)
ASCEND, 2018	217	7,740	214	7,740	1.01 (0.84, 1.22)
VITAL, 2018	148	12,933	142	12,938	1.04 (0.83, 1.31)
Overall	**1,305**	**65,431**	**1,238**	**65,278**	**1.05 (0.97, 1.13)**



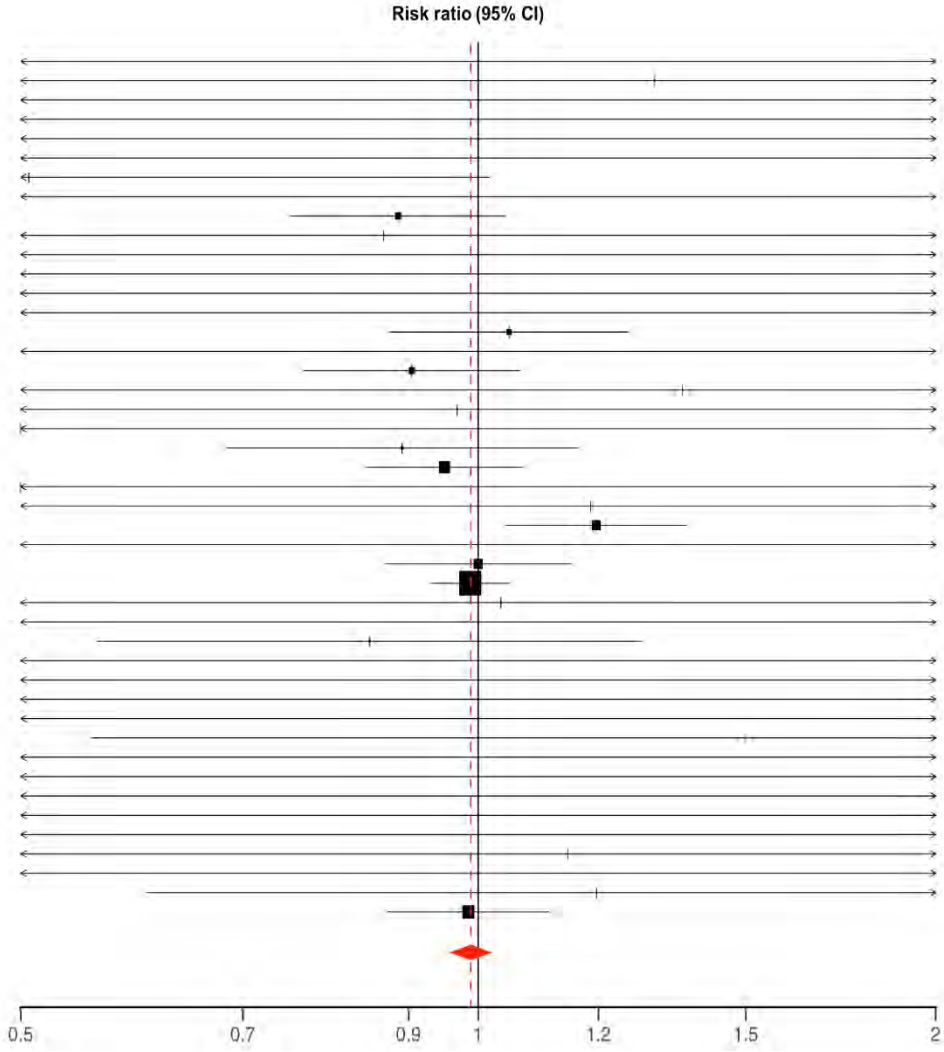
Supplement Figure 8: Forest plot showing effects of n n-3 long chain polyunsaturated fatty acids (LC PUFA) on coronary heart disease

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk ratio (95% CI)
DART, 1989	337	1,015	366	1,018	0.92 (0.82, 1.04)
Nye, 1990	5	36	11	37	0.47 (0.18, 1.21)
HARP, 1995	7	41	7	39	0.95 (0.37, 2.46)
SHOT, 1996	7	317	12	293	0.54 (0.22, 1.35)
GISSI-P, 1999	424	5,666	485	5,658	0.87 (0.77, 0.99)
SCIMO, 1999	1	112	4	111	0.25 (0.03, 2.18)
OFAMI, 2001	42	150	36	150	1.17 (0.80, 1.71)
Brox, 2001	0	80	1	40	0.17 (0.01, 4.03)
Raitt, 2005	1	100	3	100	0.33 (0.04, 3.15)
Baldassarre, 2006	1	32	0	32	3.00 (0.13, >10.0)
SOFA, 2006	1	273	3	273	0.33 (0.03, 3.18)
JELIS, 2007	262	9,326	324	9,319	0.81 (0.69, 0.95)
THIS DIET, 2008	10	51	6	50	1.63 (0.64, 4.16)
GISSI-HF, 2008	107	3,494	129	3,481	0.83 (0.64, 1.06)
ADCS, 2008	10	51	6	50	1.63 (0.64, 4.16)
OMEGA, 2009	547	1,919	568	1,885	0.95 (0.86, 1.04)
AlphaOmega EPA+DHA, 2010	122	2,404	132	2,433	0.94 (0.74, 1.19)
SU.FOL.OM3, 2010	51	1,253	53	1,248	0.96 (0.66, 1.40)
DO IT, 2010	11	282	9	281	1.22 (0.51, 2.89)
ORIGIN, 2012	344	6,281	316	6,255	1.08 (0.93, 1.26)
FORWARD, 2013	1	289	1	297	1.03 (0.06, >10.0)
EPE-A, 2014	2	168	1	75	0.89 (0.08, 9.70)
EPOCH, 2014	1	195	0	196	3.02 (0.12, >10.0)
AREDS2, 2014	28	2,147	30	2,056	0.89 (0.54, 1.49)
Doi, 2014	1	119	0	119	3.00 (0.12, >10.0)
Proudman, 2015	1	87	0	53	1.83 (0.08, >10.0)
Derosa, 2016	0	128	4	130	0.11 (0.01, 2.07)
FOSTAR, 2016	10	101	10	101	1.00 (0.44, 2.30)
ASCEND, 2018	882	7,740	887	7,740	0.99 (0.91, 1.09)
VITAL, 2018	308	12,933	370	12,938	0.83 (0.72, 0.97)
Overall	**3,524**	**56,790**	**3,774**	**56,458**	**0.93 (0.89, 0.98)**



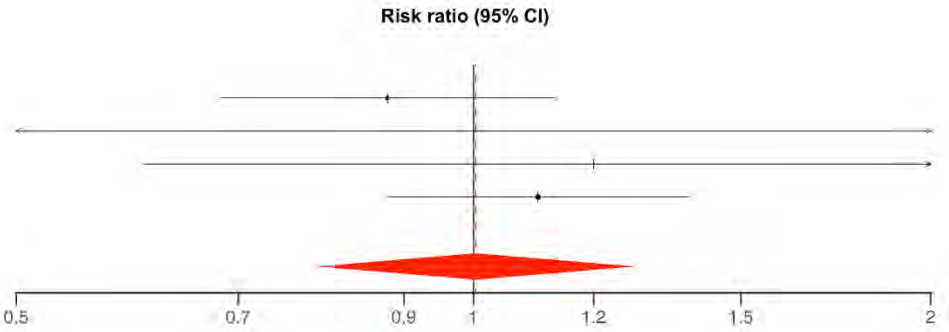
Supplement Figure 9: Forest plot showing effects of vitamin D on all-cause mortality

Study	Experimental Events	Total	Control Events	Total	Risk ratio (95% CI)
Brohult, 1973	1	25	0	25	3.00 (0.13, >10.0)
Inkovaara, 1983	7	45	5	42	1.31 (0.45, 3.80)
Corless, 1985	8	41	8	41	1.00 (0.42, 2.41)
Ott, 1989	0	43	1	43	0.33 (0.01, 7.96)
Gallagher, 1990	1	25	0	25	3.00 (0.13, >10.0)
Grady, 1991	1	50	0	48	2.88 (0.12, >10.0)
Ooms, 1995	11	177	21	171	0.51 (0.25, 1.02)
Hamdy, 1995	4	89	1	87	3.91 (0.45, >10.0)
Lips, 1996	223	1,291	251	1,287	0.89 (0.75, 1.04)
Sato, 1997	1	45	1	39	0.87 (0.06, >10.0)
Sato, 1999	1	43	0	43	3.00 (0.13, >10.0)
OSTPRE, 1999	0	112	1	115	0.34 (0.01, 8.31)
Frazao, 2000	1	71	2	67	0.47 (0.04, 5.08)
STOP IT, 2001	1	123	1	123	1.00 (0.06, >10.0)
Meyer, 2002	169	569	163	575	1.05 (0.87, 1.26)
Cooper, 2003	0	93	1	94	0.34 (0.01, 8.16)
Trivedi, 2003	224	1,345	247	1,341	0.90 (0.77, 1.07)
NONOF, 2004	7	38	5	37	1.36 (0.47, 3.91)
Dukas, 2004	1	192	1	186	0.97 (0.06, >10.0)
Sato, 2005	1	48	2	48	0.50 (0.05, 5.33)
Flicker, 2005	76	313	85	312	0.89 (0.68, 1.16)
RECORD, 2005	438	2,649	460	2,643	0.95 (0.84, 1.07)
Aloia, 2005	1	104	2	104	0.50 (0.05, 5.43)
Schleithoff, 2006	7	61	6	62	1.19 (0.42, 3.33)
Law, 2006	347	1,762	322	1,955	1.20 (1.04, 1.37)
Coyne, 2006	2	107	1	113	2.11 (0.19, >10.0)
Smith, 2007	355	4,727	354	4,713	1.00 (0.87, 1.15)
Lyons, 2007	947	1,725	953	1,715	0.99 (0.93, 1.05)
Bjorkman, 2008	10	73	9	68	1.04 (0.45, 2.39)
Prince, 2008	0	151	1	151	0.33 (0.01, 8.12)
VITAL D, 2010	40	1,131	47	1,127	0.85 (0.56, 1.28)
Janssen, 2010	1	36	0	34	2.84 (0.12, >10.0)
VITAL, 2010	1	95	0	93	2.94 (0.12, >10.0)
Grimnes, 2011	0	51	1	53	0.35 (0.01, 8.31)
Cherniack, 2011	1	23	0	23	3.00 (0.13, >10.0)
Lehouck, 2012	9	91	6	91	1.50 (0.56, 4.04)
Glendenning, 2012	2	353	0	333	4.72 (0.23, >10.0)
Alvarez, 2012	1	24	1	24	1.00 (0.07, >10.0)
TIDE, 2012	0	607	2	614	0.20 (0.01, 4.21)
Witham, 2013	1	39	0	36	2.77 (0.12, >10.0)
Hewitt, 2013	1	30	1	30	1.00 (0.07, >10.0)
Delanaye, 2013	6	22	5	21	1.15 (0.41, 3.19)
VitDISH, 2013	0	80	1	79	0.33 (0.01, 7.96)
ViDA, 2017	18	2,558	15	2,550	1.20 (0.60, 2.37)
VITAL, 2018	485	12,927	493	12,944	0.99 (0.87, 1.11)
Overall	**3,411**	**34,204**	**3,476**	**34,325**	**0.99 (0.96, 1.02)**



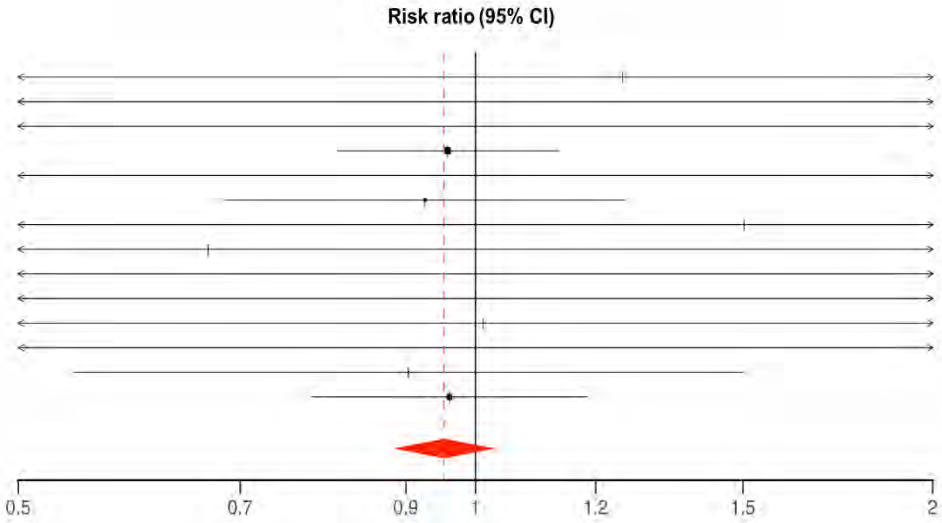
Supplement Figure 10: Forest plot showing effects of vitamin D on cardiovascular mortality

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk ratio (95% CI)
Trivedi, 2003	103	1,345	117	1,341	0.88 (0.68, 1.13)
TIDE, 2012	0	607	1	614	0.34 (0.01, 8.26)
ViDA, 2017	18	2,558	15	2,558	1.20 (0.61, 2.38)
VITAL, 2018	152	12,927	138	12,944	1.10 (0.88, 1.39)
Overall	**273**	**17,437**	**271**	**17,457**	**1.00 (0.79, 1.28)**



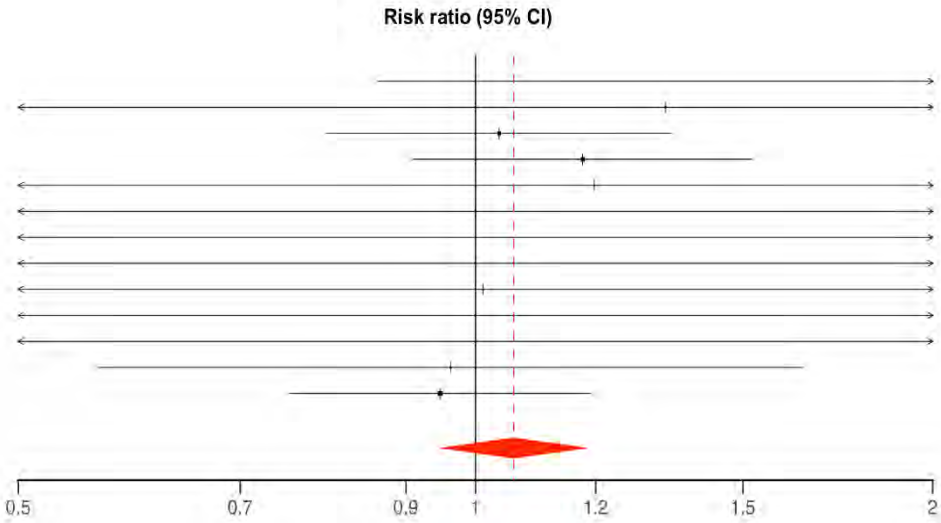
Supplement Figure 11: Forest plot showing effects of vitamin D on myocardial infarction

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk ratio (95% CI)
Aloia, 1988	1	12	1	15	1.25 (0.09, >10.0)
Ott, 1989	1	43	0	43	3.00 (0.13, >10.0)
OSTPRE, 1999	1	112	0	115	3.08 (0.13, >10.0)
Trivedi, 2003	224	1,345	233	1,341	0.96 (0.81, 1.13)
Coburn, 2004	0	27	2	28	0.21 (0.01, 4.13)
RECORD, 2005	78	2,649	84	2,643	0.93 (0.68, 1.25)
Lappe, 2007	3	445	2	446	1.50 (0.25, 8.95)
Prince, 2008	2	151	3	151	0.67 (0.11, 3.93)
VITAL, 2010	2	95	0	93	4.90 (0.24, >10.0)
Cherniack, 2011	1	23	1	23	1.00 (0.07, >10.0)
TIDE, 2012	1	607	1	614	1.01 (0.06, >10.0)
OPERA, 2014	0	30	2	30	0.20 (0.01, 4.00)
ViDA, 2017	28	2,558	31	2,558	0.90 (0.54, 1.50)
VITAL, 2018	169	12,927	176	12,944	0.96 (0.78, 1.19)
Overall	**511**	**21,024**	**536**	**21,044**	**0.95 (0.88, 1.03)**

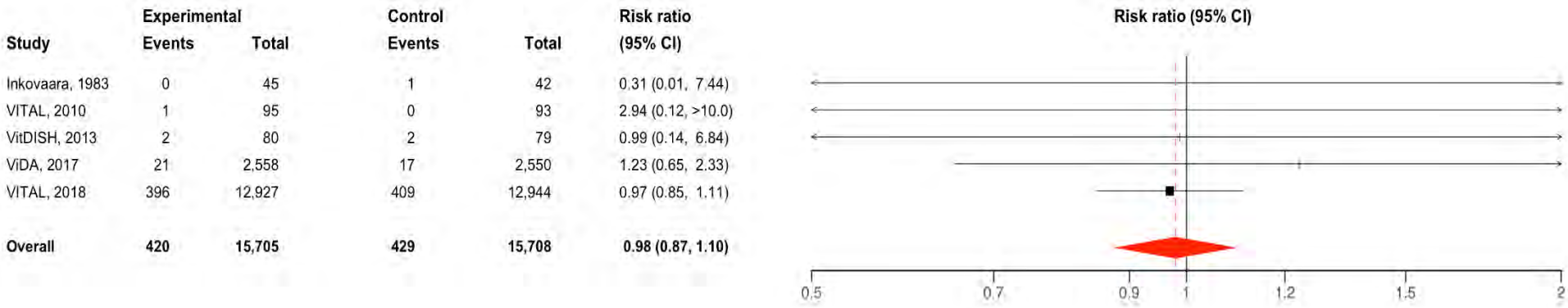


Supplement Figure 12: Forest plot showing effects of vitamin D on stroke

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk ratio (95% CI)
Inkovaara, 1983	12	45	5	42	2.24 (0.86, 5.82)
STOP IT, 2001	4	123	3	123	1.33 (0.30, 5.83)
Trivedi, 2003	105	1,345	101	1,341	1.04 (0.80, 1.35)
RECORD, 2005	118	2,549	104	2,643	1.18 (0.91, 1.52)
Lappe, 2007	6	446	5	445	1.20 (0.37, 3.89)
Prince, 2008	3	151	3	151	1.00 (0.21, 4.88)
VITAL, 2010	1	95	0	93	2.94 (0.12, >10.0)
VIDOS, 2012	1	20	0	21	3.15 (0.14, >10.0)
TIDE, 2012	1	607	1	614	1.01 (0.06, >10.0)
VitDISH, 2013	3	80	1	79	2.96 (0.31, >10.0)
OPERA, 2014	0	30	2	30	0.20 (0.01, 4.00)
ViDA, 2017	26	2,558	27	2,558	0.96 (0.56, 1.65)
VITAL, 2018	141	12,927	149	12,944	0.95 (0.75, 1.19)
Overall	**421**	**20,976**	**401**	**21,084**	**1.06 (0.95, 1.19)**



Supplement Figure 13: Forest plot showing effects of vitamin D on coronary heart disease



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REVIEW

Annals of Internal Medicine

Effects of Nutritional Supplements and Dietary Interventions on Cardiovascular Outcomes

An Umbrella Review and Evidence Map

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Background: The role of nutritional supplements and dietary interventions in preventing mortality and cardiovascular disease (CVD) outcomes is unclear.

Purpose: To examine evidence about the effects of nutritional supplements and dietary interventions on mortality and cardiovascular outcomes in adults.

Data Sources: PubMed, CINAHL, and the Cochrane Library from inception until March 2019; ClinicalTrials.gov (10 March 2019); journal Web sites; and reference lists.

Study Selection: English-language, randomized controlled trials (RCTs) and meta-analyses of RCTs that assessed the effects of nutritional supplements or dietary interventions on all-cause mortality or cardiovascular outcomes, such as death, myocardial infarction, stroke, and coronary heart disease.

Data Extraction: Two independent investigators abstracted data, assessed the quality of evidence, and rated the certainty of evidence.

Data Synthesis: Nine systematic reviews and 4 new RCTs were selected that encompassed a total of 277 trials, 24 interventions, and 992 129 participants. A total of 105 meta-analyses were generated. There was moderate-certainty evidence that reduced salt intake decreased the risk for all-cause mortality in normotensive participants (risk ratio [RR], 0.90 [95% CI, 0.85 to 0.95]) and cardiovascular mortality in hypertensive participants (RR, 0.67 [CI, 0.46 to 0.99]). Low-certainty evidence showed that omega-3 long-chain polyunsaturated fatty acid (LC-PUFA) was associated with reduced risk for myocardial infarction (RR, 0.92 [CI, 0.85 to 0.99]) and coronary heart disease (RR, 0.93 [CI, 0.89 to 0.98]). Folic acid was associated with lower risk for stroke (RR, 0.80 [CI, 0.67 to 0.96]; low certainty), whereas calcium plus vitamin D increased the risk for stroke (RR, 1.17 [CI, 1.05 to 1.30]; moderate certainty). Other nutritional supplements, such as vitamin B_6, vitamin A, multivitamins, antioxidants, and iron and dietary interventions, such as reduced fat intake, had no significant effect on mortality or cardiovascular disease outcomes (very low– to moderate-certainty evidence).

Limitations: Suboptimal quality and certainty of evidence.

Conclusion: Reduced salt intake, omega-3 LC-PUFA use, and folate supplementation could reduce risk for some cardiovascular outcomes in adults. Combined calcium plus vitamin D might increase risk for stroke.

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Current U.S. dietary guidelines recommend several healthy eating patterns, including U.S., Mediterranean, and vegetarian diets (1). Although the guidelines recognize the occasional need for nutritional supplementation or food fortification for specific nutrients that may be consumed in inadequate amounts, they do not recommend routine use of any dietary supplement to reduce risk for cardiovascular disease (CVD) or other chronic diseases. Despite these recommendations, most U.S. adults use supplements to enhance their diets, with uncertain health benefits (2, 3). From 1999 to 2012, the NHANES (National Health and Nutrition Examination Survey) reported that 52% of participants used at least 1 and 10% used at least 4 dietary supplements (4). From 2011 to 2014, the NHANES reported that among participants aged 60 years or older, 70% used at least 1 and 29% used at least 4 supplements, and 41% of supplement takers reported that they did so to improve their overall health (5).

In 2013, the U.S. Preventive Services Task Force conducted a systematic review of the utility of vitamin and mineral supplements for CVD prevention and found little evidence to support use (6). More recently, Jenkins and colleagues published a meta-analysis of randomized controlled trials (RCTs) of dietary supplements published through October 2017 (7). They found some stroke benefit conferred by folate; no CVD benefit for multivitamins, vitamin C, vitamin D, or calcium; and evidence for mortality harm for niacin and antioxidants. Since then, several landmark RCTs evaluating the efficacy of fish oils (8–10) and vitamin D (11, 12) for CVD prevention have been published, which add to the evidence level. In addition, the quality of the evidence base of these various nutritional supplements and dietary interventions still needs to be evaluated to ascertain the confidence in their efficacy. Thus, we per-

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formed a systematic review of existing meta-analyses of RCTs and generated an evidence map for efficacy of nutritional supplements and dietary interventions for CVD prevention.

METHODS

Search Strategy

We used PubMed, CINAHL, and the Cochrane Library from inception to March 2019 to find meta-analyses published in the English language about vitamins, minerals, dietary supplements or products, and dietary interventions using the following search terms: (**minerals* OR **vitamins* OR **diet* AND **cardiovascular outcomes*) and (*meta-analy** OR *metaanaly** OR *systematic review**). After selecting systematic reviews on the basis of a priori criteria, the search timelines of the systematic reviews were reviewed for recency and an updated search for RCTs published in English was performed starting from the end date of searches from selected systematic reviews until March 2019 (**Supplement Table 1**, available at Annals.org). Additional sources included Web sites of major cardiovascular and medicine journals (www.onlinejacc.org; https://academic.oup.com/eurheartj; www.ahajournals.org/journal/circ; www.nejm.org; https://jamanetwork.com; and http://annals.org/aim) and bibliographies of relevant studies. We also searched ClinicalTrials.gov (10 March 2019) to check for publication bias and to identify any new or ongoing trials (**Supplement Table 2**, available at Annals.org).

Study Selection

The prespecified inclusion criteria were meta-analyses of RCTs assessing efficacy of nutritional supplements (vitamins, minerals, dietary supplements) or dietary interventions in adult participants (≥18 years) that report effect estimates for all-cause mortality and cardiovascular outcomes of interest and were written in English. Because the nutritional and dietary recommendations are universal, there were no restrictions on baseline health status, race, or sex of the participants.

Meta-analyses of observational studies or those reporting efficacy of interventions on surrogate or other outcomes, such as blood pressure, lipid values, inflammatory markers, electrolytes, renal values, or quality-of-life indicators, were excluded. Systematic reviews reporting meta-analyses of both clinical trials and observational studies were reviewed for data related to RCTs only. In case of multiple meta-analyses of the same intervention and outcome, we preferred the most recent, largest, and updated meta-analysis. However, the competing meta-analyses were screened for any additional trials not included in the selected meta-analysis.

After removing duplicates and following the selection criteria, we screened the retrieved articles at the title and abstract level and then at the methods level. The search, selection, and abstraction processes were performed independently by 2 authors (M.U.K. and S.V.). Any discrepancies were resolved by discussion and mutual consensus, referring to the original study or third-party review (S.U.K.).

Data Extraction, Outcomes, and Quality Assessment

We first extracted information from eligible meta-analyses on first author, journal, year of publication, interventions, outcomes of interest, number of trials, whether an appropriate study search and selection criteria was reported, method of pooling estimates (fixed or random effects), methods of detecting publication bias, measure of heterogeneity, and risk-of-bias assessment. Second, we generated the pool of clinical trials by identifying trials contained in the selected meta-analyses and screening competing meta-analyses for additional trials and trials published after the selected meta-analyses (**Supplement Table 3**, available at Annals.org). Among new clinical trials for omega-3 long-chain polyunsaturated fatty acid (LC-PUFA) (8–10), we excluded REDUCE-IT (Reduction of Cardiovascular Events With EPA-Intervention Trial) (9) because icosapent ethyl, a highly purified form of eicosapentaenoic acid (EPA), does not qualify as a dietary supplement according to the Dietary Supplement Health and Education Act of 1994 (13). Third, after removing duplicates, we abstracted data on trial name, first author, year, intervention, outcomes, raw events, and sample sizes for each group.

The main outcome of interest was all-cause mortality. The secondary outcomes were cardiovascular mortality, myocardial infarction (MI), stroke, and coronary heart disease (CHD).

Two independent reviewers (V.O. and M.S.K.) assessed the methodological quality of meta-analyses on specific potential factors that may affect the validity of summary estimates—that is, appropriate search and selection criteria, number of trials and participants included, risk-of-bias assessment of included trials, method of pooling the estimates, assessment of publication bias, and degree of heterogeneity (**Supplement Table 4**, available at Annals.org).

Data Synthesis and Analysis

We created an evidence map that displays the plausible benefits of each intervention and the certainty of the evidence (14). The certainty of the evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (GRADEpro GDT) (https://gdt.gradepro.org/app/) (14) and was classified as high, moderate, low, or very low (**Supplement Table 5**, available at Annals.org). Two reviewers (V.O. and M.S.K.) performed these assessments under the supervision of a third reviewer (S.U.K.).

Estimates were pooled according to Mantel–Haenszel random-effects model. The Paule–Mandel method was used for reestimating outcomes. Hartung–Knapp small-sample adjustments were applied when the number of studies was less than 10 (15). Effect sizes were reported as risk ratios (RRs) with 95% CIs. We used I^2 statistics to estimate the extent of unexplained heterogeneity; I^2 greater than 50% was considered a high degree of between-study heterogeneity. We calculated the Egger regression test as an estimate of publication

bias for any reanalysis that included at least 10 studies (16).

Statistical analyses were conducted using "meta," version 4.9-4 (R Project for Statistical Computing). Statistical significance was set at 0.05 for all analyses except for the Egger regression test, which had a threshold less than 0.10 because of the test's limited statistical power.

Role of the Funding Source

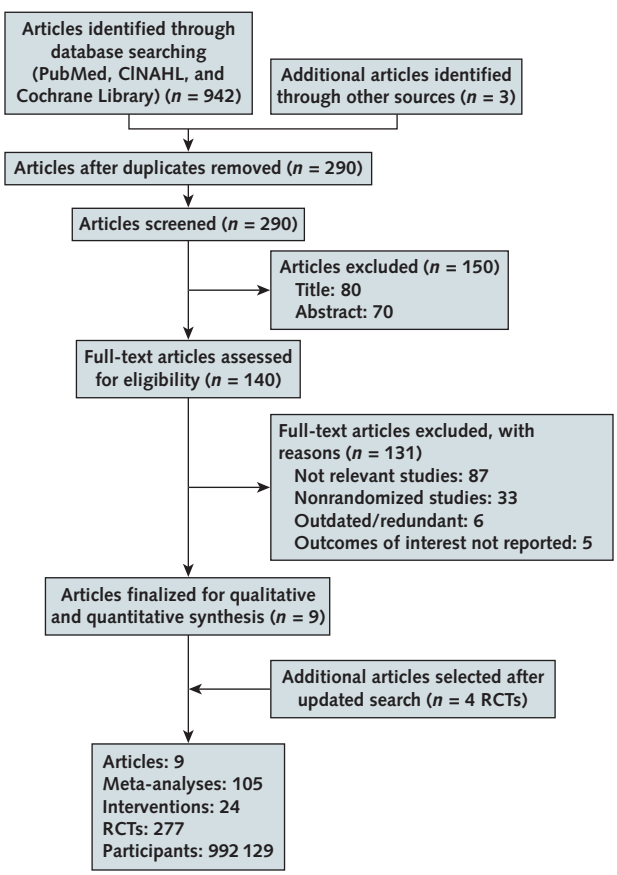
The study received no funding.

RESULTS

Search Results

Of 942 citations, after removing duplicates and screening at the title and abstract level we reviewed 140 full-text articles for eligibility. We excluded 131 articles because they focused on nonrandomized studies, were not relevant, or were outdated, as well as 5 systematic reviews that assessed intake of nuts (17), fruits and vegetables (18), fiber (19), and green or black tea (20) and those focusing on low-carbohydrate and low-fat diets (21) that did not report cardiovascular outcomes of interest. Ultimately, we included 9 systematic reviews and 4 new RCTs for a total of 105 meta-analyses of 24 interventions (277 RCTs, 992 129 participants) (7, 22–29) (Figure 1). The interventions evaluated in the meta-analyses included 16 types of supplements (antioxidants, β-carotene, vitamin B complex, multivitamins, selenium, vitamin A, vitamin B_3 or niacin, vitamin B_6, vitamin C, vitamin E, vitamin D, calcium plus vitamin D, calcium, folic acid, iron, and omega-3 LC-PUFA) and 8 types of dietary interventions (Mediterranean diet and intake of reduced saturated fat, modified dietary fat, reduced dietary fat, reduced salt among hypertensive and normotensive participations, increased omega-3 α-linolenic acid [ALA], and increased omega-6 PUFA) (Supplement Table 6, available at Annals.org).

Figure 1. Evidence search and selection.



RCT = randomized controlled trial.

Quality Assessment

All included studies were trial-level meta-analyses (7, 22–28), except the study by Mente and colleagues, which was a patient-level analysis of 4 studies (29) (Supplement Table 4). All trial-level systematic reviews reported comprehensive search and selection criteria as well as quality assessment of studies by using the Cochrane Risk of Bias Tool (30). Six systematic reviews primarily used random-effects models for meta-analyses, of which 4 used fixed-effects models for sensitivity analyses. Two studies primarily used fixed-effects models, of which 1 selected a random-effects model only for estimates with an I^2 greater than 50%. Out of all trial-level analyses, only 2 did not assess publication bias, and 1 did not evaluate between-study variance because of the limited number of trials (<10). Eighty-one (77%) meta-analyses included fewer than 10 trials. Thirty-six (34%) meta-analyses included fewer than 84% double-blind RCTs; of these, 3 (2.8%) had a total sample of fewer than 1000 participants, 16 (15%) had I^2 greater than 50%, and 4 (3.8%) had significant publication bias.

All-Cause Mortality

All 24 interventions assessed the risk for all-cause mortality. Reduced salt intake in normotensive participants was found to reduce risk (RR, 0.90 [95% CI, 0.85 to 0.95]; $P = 0.01$; $I^2 = 0\%$; moderate certainty) (Figure 2). Other nutritional supplements or dietary interventions had no association with risk for this outcome. The Egger regression test was consistent with publication bias for omega-3 LC-PUFA ($P = 0.09$) and reduced saturated fat intake for all-cause mortality ($P = 0.02$) (Supplement Table 7, available at Annals.org).

Cardiovascular Mortality

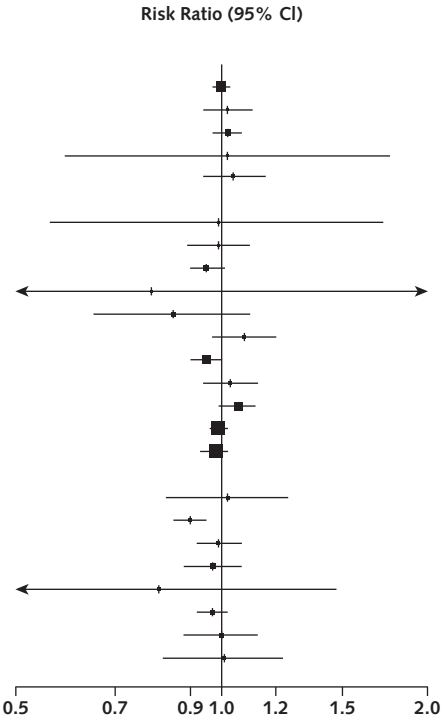
Twenty-one interventions assessed the risk for cardiovascular mortality. Reduced salt intake in hypertensive participants reduced risk (RR, 0.67 [CI, 0.46 to 0.99]; $P = 0.04$; $I^2 = 0\%$; moderate certainty) (Figure 3). Other nutritional supplements or dietary interventions were not associated with risk for this outcome.

MI

Twenty-one interventions assessed risk for MI. Use of omega-3 LC-PUFA was associated with reduced risk (RR, 0.92 [CI, 0.85 to 0.99]; $P = 0.03$; $I^2 = 1\%$; low certainty) (Supplement Figure 1, available at Annals.org). Other nutritional supplements or dietary interventions

Figure 2. Effects of nutritional supplements and dietary interventions on all-cause mortality.

Intervention	Author, Year (Reference)	Studies, *n*	Events, *n*	Participants, *n*	Risk Ratio (95% CI)
Nutritional supplements					
Vitamin E	Jenkins et al, 2018 (7)	32	8984	123 001	1.00 (0.97–1.03)
Vitamin C	Jenkins et al, 2018 (7)	4	1819	16 004	1.02 (0.94–1.11)
Vitamin B complex	Jenkins et al, 2018 (7)	16	6245	45 424	1.02 (0.97–1.07)
Vitamin B_6	Jenkins et al, 2018 (7)	2	239	3429	1.02 (0.59–1.76)
Vitamin B_3/niacin	Jenkins et al, 2018 (7), and Riaz et al, 2019 (28)	5	2694	33 246	1.04 (0.94–1.16)
Vitamin A	Jenkins et al, 2018 (7)	1	48	2297	0.99 (0.56–1.72)
Selenium	Jenkins et al, 2018 (7)	4	992	19 373	0.99 (0.89–1.10)
Multivitamins	Jenkins et al, 2018 (7)	10	3633	22 869	0.95 (0.90–1.01)
Iron	Jenkins et al, 2018 (7)	2	35	762	0.79 (0.16–3.85)
Folic acid	Jenkins et al, 2018 (7)	10	877	25 580	0.85 (0.65–1.10)
Calcium	Jenkins et al, 2018 (7)	6	1084	9765	1.08 (0.97–1.20)
Calcium plus vitamin D	Jenkins et al, 2018 (7)	20	3690	42 072	0.95 (0.90–1.00)
β-Carotene	Jenkins et al, 2018 (7)	6	4284	42 342	1.03 (0.94–1.13)
Antioxidants	Jenkins et al, 2018 (7)	21	8472	105 780	1.06 (0.99–1.12)
Vitamin D	Khan et al, 2019*	45	6887	68 529	0.99 (0.96–1.02)
omega-3 LC-PUFA	Khan et al, 2019*	41	10 707	134 034	0.98 (0.93–1.02)
Dietary interventions					
Modified dietary fat	Hooper et al, 2011 (26)	8	1120	11 441	1.02 (0.83–1.25)
Reduced salt (normotensive)	Adler et al, 2014 (22)	3	79	3518	0.90 (0.85–0.95)
Reduced salt (hypertensive)	Adler et al, 2014 (22)	5	674	3680	0.99 (0.92–1.07)
Reduced saturated fat	Hooper et al, 2015 (27)	12	3276	55 858	0.97 (0.88–1.07)
Mediterranean diet	Liyanage et al, 2016 (23)	5	693	10 671	0.81 (0.45–1.47)
Reduced dietary fat	Hooper et al, 2011 (26)	10	2936	58 130	0.97 (0.92–1.02)
omega-6 PUFA	Hooper et al, 2018 (25)	10	740	4506	1.00 (0.88–1.13)
omega-3 ALA PUFA	Abdelhamid et al, 2018 (24)	5	459	19 327	1.01 (0.82–1.23)



ALA = α-linolenic acid; LC-PUFA = long-chain polyunsaturated fatty acid.
* Updated meta-analysis after inclusion of new clinical trials.

had no association with risk for this outcome. The Egger regression test was consistent with publication bias for meta-analyses of vitamin E (P = 0.01) (Supplement Table 7).

Stroke

Twenty interventions assessed the risk for stroke. Folic acid was associated with lower risk (RR, 0.80 [CI, 0.67 to 0.96]; P = 0.02; I^2 = 0%; low certainty), whereas combined calcium plus vitamin D intake was associated with increased risk (RR, 1.17 [CI, 1.05 to 1.30]; P = 0.01; I^2 = 0%; moderate certainty) (Supplement Figure 2, available at Annals.org). Other nutritional supplements or dietary interventions had no association with risk for this outcome. The Egger regression test was consistent with publication bias for meta-analyses of vitamin E (P = 0.08) (Supplement Table 7).

CHD

Nineteen interventions assessed the risk for CHD. Use of omega-3 LC-PUFA was associated with reduced risk (RR, 0.93 [CI, 0.89 to 0.98]; P = 0.01; I^2 = 2%; low certainty) (Supplement Figure 3, available at Annals.org). There was no association between other nutritional supplements or dietary interventions with risk for CHD.

Evidence Map

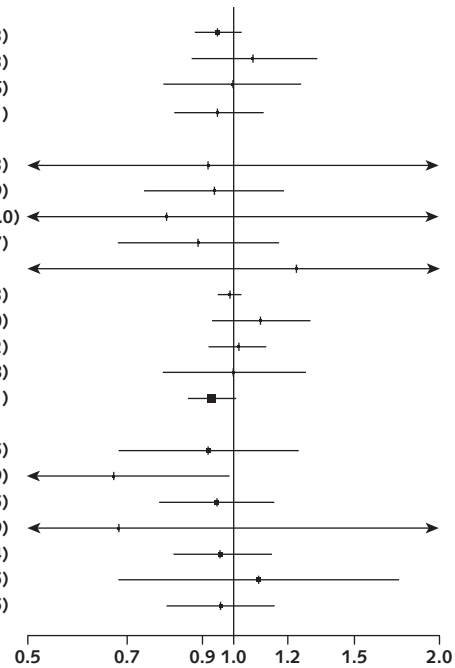
Figure 4 is an evidence map summarizing the findings for included interventions. There is a paucity of data assessing the effects of vitamin B_6, vitamin A, multivitamins, iron, antioxidants, and reduced salt intake on certain cardiovascular end points. The map also shows the lack of significant effects on all-cause mortality and cardiovascular outcomes for most nutritional supplements, that the certainty of evidence varies from very low to low for most of the interventions, and that none of the interventions have high-quality evidence.

DISCUSSION

In this overview of 24 nutritional supplements and dietary interventions evaluating data from RCTs and meta-analyses of RCTs, we found some evidence that reduced salt intake was protective for all-cause mortality in normotensive participants and cardiovascular mortality in hypertensive participants, that omega-3 LC-PUFA was protective for MI and CHD, and folic acid was protective for stroke. Conversely, combined calcium plus vitamin D intake increased the risk for stroke. Other supplements, such as multivitamins, selenium, vitamin A, vitamin B_6, vitamin C, vitamin E, vitamin D alone, calcium alone, folic acid, and iron, or such dietary interventions as the Mediterranean diet, reduced saturated fat intake, modified fat intake, reduced dietary fat intake, and increased intake of omega-3 ALA or omega-6 PUFA, did not seem to have a significant effect on mortality or CVD outcomes (with very low– to moderate-certainty evidence).

Figure 3. Effects of nutritional supplements and dietary interventions on cardiovascular mortality.

Intervention	Author, Year (Reference)	Studies, *n*	Events, *n*	Participants, *n*	Risk Ratio (95% CI)
Nutritional supplements					
Vitamin E	Jenkins et al, 2018 (7)	11	2887	102 533	0.95 (0.88–1.03)
Vitamin C	Jenkins et al, 2018 (7)	2	646	15 497	1.07 (0.87–1.33)
Vitamin B complex	Jenkins et al, 2018 (7)	5	2642	33 693	1.00 (0.79–1.26)
Vitamin B_3/niacin	Jenkins et al, 2018 (7), and Riaz et al, 2019 (28)	4	958	7677	0.95 (0.82–1.11)
Selenium	Jenkins et al, 2018 (7)	3	346	18 851	0.92 (0.15–5.63)
Multivitamins	Jenkins et al, 2018 (7)	3	984	17 351	0.94 (0.74–1.19)
Iron	Jenkins et al, 2018 (7)	2	31	760	0.80 (0.03–>10.0)
Folic acid	Jenkins et al, 2018 (7)	5	188	22 468	0.89 (0.68–1.17)
Calcium	Jenkins et al, 2018 (7)	2	47	2931	1.24 (0–>10.0)
Calcium plus vitamin D	Jenkins et al, 2018 (7)	1	510	36 282	0.99 (0.95–1.03)
β-Carotene	Jenkins et al, 2018 (7)	4	1191	33 668	1.10 (0.93–1.30)
Antioxidants	Jenkins et al, 2018 (7)	7	2263	49 729	1.02 (0.92–1.12)
Vitamin D	Khan et al, 2019*	4	544	34 894	1.00 (0.79–1.28)
omega-3 LC-PUFA	Khan et al, 2019*	27	5270	109 123	0.93 (0.86–1.01)
Dietary interventions					
Modified dietary fat	Hooper et al, 2011 (26)	6	593	10 788	0.92 (0.68–1.25)
Reduced salt (hypertensive)	Adler et al, 2014 (22)	3	106	2656	0.67 (0.46–0.99)
Reduced saturated fat	Hooper et al, 2015 (27)	12	1096	53 421	0.95 (0.78–1.15)
Mediterranean diet	Liyanage et al, 2016 (23)	4	315	10 623	0.68 (0.21–2.19)
Reduced dietary fat	Hooper et al, 2011 (26)	7	602	52 971	0.96 (0.82–1.14)
omega-6 PUFA	Hooper et al, 2018 (25)	7	472	4019	1.09 (0.68–1.75)
omega-3 ALA PUFA	Abdelhamid et al, 2018 (24)	4	219	18 619	0.96 (0.80–1.15)



ALA = α-linolenic acid; LC-PUFA = long-chain polyunsaturated fatty acid.
* Updated meta-analysis after inclusion of new clinical trials.

The beneficial effects of reduced salt intake on mortality and CVD risk reduction remain a debatable issue. Although some data support lower salt intake to reduce CVD risk (31, 32), other studies have shown a U-shaped relationship between sodium intake and death (33–35). Recently, 2 studies explored the relationship between measures of sodium intake, estimated from urinary sodium excretion and death (29, 32). A patient-level study of 4 prospective studies (133 118 participants) concluded that reduced intake of sodium should be confined to hypertensive patients only who also consume high sodium (29). However, Cook and colleagues reported a higher risk for all-cause mortality with increased sodium intake in participants of the TOHP (Trials of Hypertension Prevention) and showed the benefit of reduced sodium intake on death during a period of 20 years (32).

The mechanism behind the benefit of reduced salt intake on death is most likely related to reduced blood pressure. Hypertension is a known risk factor for CVD, and scientific evidence exists of a direct relationship between dietary salt intake and blood pressure (36–38). A meta-analysis of 34 trials (3230 participants) showed that reduction in salt intake (an average of 4.4 g/d) was associated with reduced systolic and diastolic blood pressures in both hypertensive and normotensive patients, regardless of sex or ethnicity (36). This benefit can potentially translate into cardiovascular risk reduction. It was estimated that lowering salt intake to 6 g per day would be associated with a reduction in systolic blood pressure by about 7 mm Hg and a reduction in diastolic blood pressure by about 4 mm Hg in hypertensive patients and approximately 4 and 2 mm Hg, respectively, in normotensive patients; in turn, this could predict reduction in stroke rates by 24% and CHD by 18% (36, 39).

Clinical trials of omega-3 LC-PUFA have shown conflicting results regarding reduction of cardiovascular outcomes. However, recent randomized data have shown cardiovascular benefits (8–10). Although VITAL (Vitamin D and Omega-3 Trial) (8) and ASCEND (A Study of Cardiovascular Events iN Diabetes) (10) did not find convincing evidence of protective effects of omega-3 LC-PUFA for overall cardiovascular benefits (primary outcomes), VITAL did show a benefit of omega-3 LC-PUFA at 1 g per day for the reduction of MI, a secondary outcome (8). Moreover, VITAL showed a 19% reduction in major CVD outcomes among the subgroup of participants with low dietary fish intake (8).

Even more notable was the recent publication of the landmark REDUCE-IT, that found, compared with placebo, a remarkable 25% reduction in cardiovascular end points with the use of icosapent ethyl, a modified and highly purified form of EPA (9). This trial studied a much higher dose of EPA (4 g/d) than previous studies and included high-risk participants (those with known atherosclerotic CVD or diabetes mellitus and at least 1 additional vascular risk factor) who had controlled low-density lipoprotein cholesterol while receiving statin therapy but had elevated triglyceride levels (135 to 499

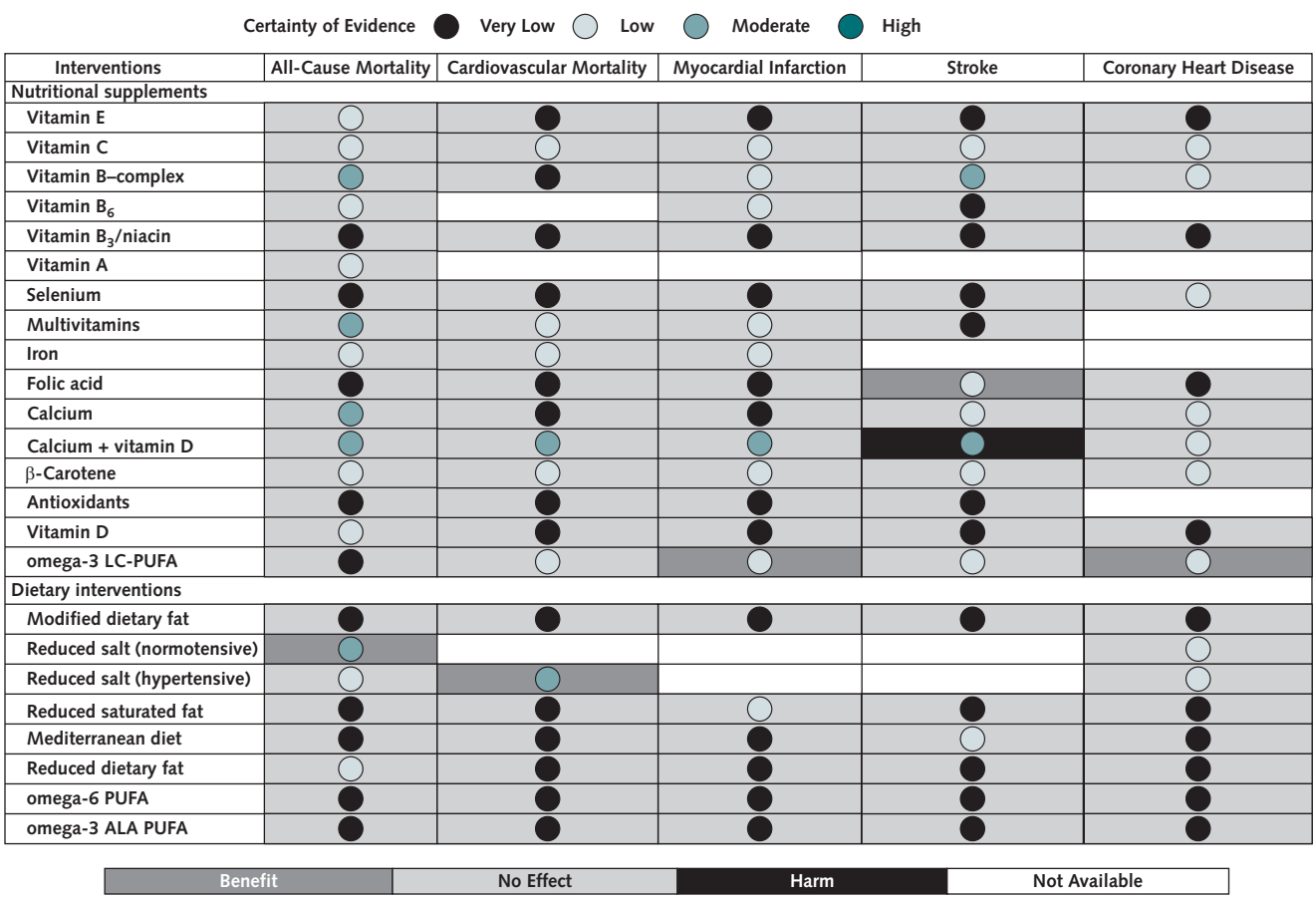
mg/dL) (9). As the cardiovascular risk reduction seen with icosapent ethyl exceeded the anticipated benefits from triglyceride reduction alone, other potential beneficial mechanisms, such as anti-inflammatory or antithrombotic effects, have been speculated. Icosapent ethyl is proprietary and is available only by prescription. It is unclear whether the effects observed in REDUCE-IT are specific for icosapent ethyl or reflect use of the higher dose of omega-3 LC-PUFA. The results should thus not be generalized to dietary supplement formulations of omega-3 LC-PUFA, which are unregulated and have variable composition (typically EPA plus docosahexaenoic acid).

Folate supplementation was associated with a lower risk for stroke, but this was largely driven by the results of the CSPPT (China Stroke Primary Prevention Trial), which evaluated the efficacy of folic acid therapy for primary prevention of stroke among hypertensive adults in China (40). This benefit might be due to the lack of folate fortification of foods in China (7), and whether these results can be generalized to a population, such as the United States, which has folate fortification, remains unclear.

On the other hand, we found that combined calcium plus vitamin D supplementation resulted in a higher risk for stroke. In a reanalysis of the WHI CaD Study (Women's Health Initiative Calcium/Vitamin D Supplementation Study), risk for cardiovascular events, including stroke, was higher in women allocated to calcium plus vitamin D administration who were not taking personal calcium supplements (41). Potential biological explanations are hypercalcemia-mediated vascular calcifications, triggering of atherosclerosis, and hypercoagulability (42, 43). Of note, a recent observational analysis from NHANES found that use of calcium supplements was associated with an increased risk for death from cancer (2). Another analysis found an association with increased risk for MI (44). These findings, along with our findings from RCTs regarding stroke risk, raise concerns about harms from calcium supplement use. Regarding vitamin D alone (without calcium), despite new RCT data from the VITAL (11) and ViDA (Vitamin D Assessment Study) (12) trials, there was no evidence found for benefit or harm for vitamin D supplementation and CVD risk reduction.

Regarding multivitamins, our review was consistent with a previous meta-analysis (3) and supports the statements by the U.S. Preventive Services Task Force in 2014 regarding the lack of adequate evidence to support the benefit of multivitamin supplementation for CVD or death (6, 45). The lack of benefit of dietary sup-

Figure 4. Evidence map of availability and appraisal of certainty of the evidence.



ALA = α-linolenic acid; LC-PUFA = long-chain polyunsaturated fatty acid.

plements on death was also seen in a recent observational study from NHANES (2).

Regarding dietary recommendations from food sources, the American Heart Association (46) and the 2015 to 2020 U.S. dietary guidelines suggest limiting saturated fats and trans fats as a "key recommendation" for promoting a healthy lifestyle. The Mediterranean diet has been shown to be effective in reducing cardiovascular risk (23), but concerns have been raised regarding the methodological validity of some of the RCT studies. For instance, the Indo-Mediterranean study generated considerable controversy because of the lack of trained professionals required to run a trial of scientific validity (47). Similarly, the PREDIMED (Prevención con Dieta Mediterránea) (48) study was retracted and republished after errors in random assignment were found, although the conclusions were largely unchanged in the reanalysis. In our analysis, the Mediterranean diet, modified dietary fat, reduced dietary fat, reduced saturated fat intake, omega-6 PUFA, or omega-3 ALA PUFA did not reduce the risk for mortality or cardiovascular outcomes.

We compared our results with previous meta-analyses identified in our searches. Graudal and colleagues (274 683 patients) concluded that both low and high salt intake were associated with higher risk for all-cause mortality (35). However, their results were predominantly based on observational studies (23 cohort studies and 2 follow-up studies of RCTs). Conversely, Adler and colleagues showed little evidence for cardiovascular mortality reduction with lowered salt intake among hypertensive patients (RR, 0.67 [CI, 0.45 to 1.01]), which did not achieve statistical significance (22). We included the same clinical trials, but the discrepancy in results may be due to the different analytic approach used in the meta-analyses. Adler and colleagues used a fixed-effects model to analyze the results, whereas our meta-analysis was conducted using a more robust Paule–Mandel estimator with Hartung–Knapp adjustments (15). The same explanation applies to differences in results related to multivitamins and minerals from a recent meta-analysis by Jenkins and colleagues (7), except for folic acid, where we are in accord with Jenkins and colleagues' findings. Abdelhamid and colleagues suggested benefit of omega-3 LC-PUFA in reducing CHD risk (RR, 0.93 [CI, 0.88 to 0.97]) but found no statistically significant effect on MI (24). Another meta-analysis by Aung and colleagues (10 RCTs, 77 917 participants) showed that omega-3 LC-PUFA supplementation was not associated with prevention of fatal CHD or CVD events (49). Our analysis is updated with recent data through March 2019, which explains the difference in results for omega-3 LC-PUFA compared with earlier reviews (8, 10, 24, 49). Regarding the higher risk for stroke due to combined calcium plus vitamin D, our results are consistent with a previous meta-analysis (41).

Our study's strengths included using data only from RCTs and their meta-analyses, considering both dietary interventions and dietary supplements, and incorporating new trial data published in 2018 and 2019 after prior meta-analyses. The U.S. Department of Health and Human Services and the U.S. Department of Agriculture have been criticized for the paucity of sound scientific background behind their dietary recommendations (50). Similarly, the U.S. Preventive Services Task Force report has not been updated since 2014 (45). Our review provides a direct quantitative comparison of various nutritional and dietary interventions for cardiovascular outcomes. Because our generated evidence map is derived from RCTs, this report can assist to cover the "evidence-free zone" in this field (50).

Nevertheless, our findings need to be considered in the context of certain limitations. There are inherent limitations secondary to the shortcomings of included meta-analyses and RCTs (that is, heterogeneity of baseline characteristics of the participants, including age, sex, health and socioeconomic status, and interventions; lack of dose–response analyses; and variable duration of follow-up). Because the focus of our study was to provide broad-based evidence for various nutritional supplements and dietary interventions using existing meta-analyses and trial-level information, we could not analyze interventions according to important subgroups, such as sex, body mass index, lipid values, blood pressure thresholds, diabetes, and history of CVD. Various meta-analyses pooled a smaller number of trials, leading to the risk for small-study effects (51), and were limited by trials that were not double blind, lacked robust methods of pooling estimates, and had publication bias. Using the GRADE system, we found that the certainty of evidence was generally low or very low. Issues related to precision of the estimates, indirectness, quantitative and qualitative heterogeneity, and publication bias resulted in generally low-quality evidence.

In summary, this overview of the efficacy of nutritional supplements and dietary interventions on mortality and cardiovascular outcomes found evidence that supports reduced salt intake, omega-3 LC-PUFA intake, and folate supplementation for CVD risk reduction. Conversely, combined calcium plus vitamin D showed an increased risk for stroke. Other vitamins, minerals, dietary supplements, and dietary interventions were not associated with survival or cardiovascular benefits. Overall, these findings are limited by suboptimal quality of the evidence. This study can help those who create professional cardiovascular and dietary guidelines modify their recommendations, provide the evidence base for clinicians to discuss dietary supplements with their patients, and guide new studies to fulfill the evidence gap.

From West Virginia University, Morgantown, West Virginia (S.U.K., M.U.K., S.V.); Cleveland Clinic, Cleveland, Ohio (H.R.); Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (D.Z.); East Carolina University, Greenville, North Carolina (L.V., V.O.); Mayo Clinic, Rochester, Minnesota (I.B.R., M.H.M.); John H. Stroger, Jr. Hospital of Cook County, Chicago, Illinois (M.S.K.); Guthrie Robert Packer Hospital, Sayre, Pennsylvania (E.K.); Johns Hopkins School of Medicine, Baltimore, Maryland (M.J.B.); Johns Hopkins Bloomberg School of

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